Over the last 40 years improvements in detection and treatment have revolutionised cancer medicine and we’ve seen survival rates double. Yet despite these advances, there remain groups for whom outcomes are particularly poor, including those with lung cancer.

Lung cancer is the second most common cancer in the UK, with over 40,000 people diagnosed each year. It has one of the lowest rates of survival - fewer than 10% of patients survive five years after diagnosis - and improvements have been limited in recent decades.

Growing the quality and quantity of lung cancer research in the UK is vital, and Cancer Research UK is committed to increasing our investment and focus to meet the urgent need for progress.

We are establishing the Cancer Research UK Lung Cancer Centres of Excellence to provide strong scientific leadership in the field, and to recruit and develop vital expertise.

The first Centre, jointly based in Manchester and UCL, will combine strengths across the spectrum of lung cancer research with state-of-the-art technology. It will catalyse new approaches to prevention, diagnosis and therapy to have the greatest impact.

We believe our investment provides an ideal platform for making progress by building the long-term capacity, environment and infrastructure for lung cancer research today that will save lives tomorrow.
We are delighted to have been chosen as Cancer Research UK’s first Lung Cancer Centre of Excellence. The establishment of the CRUK Lung Cancer Centre of Excellence at Manchester and UCL brings together a unique range of internationally renowned scientists and clinicians within the field of lung cancer research. By building on this existing foundation, we will create an environment that catalyses imaginative and innovative lung cancer research.

Research within the Centre is focused around eight complementary and interacting research themes: Basic Science, Immunology, Drug Discovery, Early Detection and Pre-Invasive Disease, Tumour Evolution and Heterogeneity, Biomarkers, Clinical Trials and Radiation Biology/Radiotherapy Trials. We aim to detect and diagnose lung cancer earlier; better predict risk of recurrence post-surgery; monitor disease non-invasively with biomarker testing and control re-emergent and advanced disease through personalised therapy. These aims can only be realised through improved knowledge of lung cancer genetics, biology and tumour adaptation to therapeutic intervention.

We are committed to delivering an outstanding lung cancer training programme and building a world class centre of excellence in lung cancer research.

The establishment of the CRUK Lung Cancer Centre of Excellence at Manchester and UCL recognises our strong track record, expertise and ambition in all aspects of lung cancer research. By working together, we have a real and exciting opportunity to support advances in the prevention, diagnosis, treatment and care of lung cancer, with our ultimate aim to improve outcomes for lung cancer patients.

INTRODUCTION
RESEARCH THEMES
RESEARCH THEMES

The CRUK Lung Cancer Centre of Excellence at Manchester and UCL brings together world class basic, translational, clinical and imaging research, with the overall vision of improving outcomes for lung cancer patients.

Our work is focused on eight key research themes:

- Basic Science
- Immunology
- Drug Discovery
- Early Detection and Pre-Invasive Disease
- Tumour Evolution and Heterogeneity
- Biomarkers
- Clinical Trials
- Radiation Biology/ Radiotherapy Trials

Each of the Centre’s research themes has joint leads based at Manchester and UCL, who are together responsible for developing and implementing the overall research strategy. These themes are designed to be both interacting and complementary and to cover the full spectrum of cancer research, linking pioneering laboratory studies to the implementation of novel treatments for patients in the clinic – with the overall aim of improving patient outcome and quality of life.

Increasingly, projects are multidisciplinary, drawing on the skills and expertise of researchers from a range of different disciplines; including pathologists, medical and radiation oncologists, biologists, chemists, physicists, bioinformaticians and engineers – allowing us to expand our research interests into innovative and exciting new areas of lung cancer research.
At present less than 20% of lung cancer patients can be stratified for treatment with targeted therapies – patients with mutationally activated kinases such as EGFR or EML4-ALK. These patients receive significant benefit from targeted therapies aimed at inhibiting these kinases specifically. The inhibition of the activated kinase suppresses proliferation and, in some cases, promotes cell death.

Nevertheless, despite significant advances in the development of targeted therapies for patients with lung cancer, many patients are either ineligible or suffer the consequences of the emergence of drug resistant disease. It is therefore evident that more powerful targeted therapies, including combination therapies, will need to be developed for successful lung cancer treatment.

To do this, it is necessary to uncover which cellular signalling pathways are responsible for resistance to current and novel therapies, and how we can overcome resistance more specifically and potently in individual cancer patients.

The approaches we currently take in Manchester and UCL are, on the one hand, to identify genetic drivers of lung cancer and lung cancer therapy resistance, with a particular focus on mutations in components of survival pathways, and, on the other, to devise targeted therapeutic combinations that specifically induce programmed cell death by apoptosis in lung cancer cells.

Regarding the first approach, we use (i) bioinformatics tools and structural modelling to evaluate the functional impact of somatic mutations in novel or understudied kinases identified in cancer genomic screens or drug resistance screens, (ii) genetic dependency screens to identify important genetically altered drivers of cancer or mediators of therapeutic resistance, and (iii) mining of cancer genomic data portals to identify frequently
amplified kinases that harbour pathological somatic mutations. The overall goal of this approach is to identify common and convergent pathways utilised by cancer cells to promote tumour growth and adaptation, which can be therapeutically targeted.

The aims of the second approach are (i) to determine the therapeutic efficacy of novel pro-apoptotic targeted therapeutic combinations in the most advanced in vivo models of lung cancer and (ii) to identify the mechanisms of resistance – and how we may be able to target them therapeutically – that characterise cancers that emerge as resistant to even the most highly effective of these therapies by multilevel data analysis which includes genomic, proteomic and tumour microenvironmental profiling.

Our ultimate aim is to determine how best to combine the inhibition of genetic drivers of lung cancer with targeted apoptosis inducing therapies in individual lung cancer patients. As such, we will investigate the interplay between the molecular alterations induced by targeting survival pathways that are upregulated in individual cancers with specific kinase inhibitory therapies and the triggering of the apoptosis machinery by targeted combination therapies. Finally, we will examine this interplay on the biochemical, genomic and proteomic level using human lung cell lines, primary human lung cancer cells and the most advanced murine in vivo models of lung cancer.

The Centre will draw on Manchester’s strengths in elucidating genetic drivers of lung cancer, with its special focus on kinases in survival pathways, and UCL’s strength in devising novel apoptosis based therapies for lung cancer, in order to develop a number of novel targeted therapies.

“Basic scientific research is an essential first step in unravelling the complex interactions that promote cancer cell survival in order to find new targets for personalised treatments specific to individuals and their disease characteristics.”
Manipulation of the patient’s own immune system to target cancer has for the first time demonstrated significant clinical efficacy against metastatic melanoma, renal cell cancer and non-small cell lung cancer. Cancer immunotherapy will play a pivotal role in improving outcomes for patients with lung cancer.

In order to improve the activity of cancer immunotherapy in a higher proportion of patients, a multifaceted approach, targeting not only the cancer cell but also the tumour microenvironment and the immune system, is likely to be essential to favour complete tumour eradication, alongside conventional approaches. The Centre will draw on the expertise of both institutions to incorporate these components in a rational and multidisciplinary bench to bedside approach.

UCL is currently leading efforts to determine heterogeneity and the potential impact of intra-tumour heterogeneity in the clinical outcome of lung cancer patients. In this scenario, the immune system is likely to play an essential role, as the same genetic instability that promotes tumour progression might also generate neo-antigens seen by the immune system as non-self, thus becoming potential targets of activated immune cells. Several research teams are bringing together the cancer and immune biology fields by investigating the interplay between the immune system and intra-tumour heterogeneity and the relevance of different immune-modulatory pathways in the control of anti-tumour immunity in human lung cancer.

In a parallel and complementary area of discovery, Manchester has developed a number of tumour models to investigate the impact of radiotherapy and immunotherapy combination approaches. Complementary to this, at UCL new ways to promote tumour apoptosis are being studied. Finally, we are using expertise in cellular therapies to develop preclinical and clinical protocols for the genetic engineering of immune cells, arming them with the necessary tools to recognise the tumour and
to function within an immunosuppressive microenvironment.

Tumour cell death induced by different agents will help reduce disease burden whilst also acting as a personalised vaccine, allowing recognition of multiple tumour antigens and neo-antigens by the immune system. In this context, incorporation of immune modulatory strategies capable of enhancing immunity should result in a long lasting, diversified and evolving layer of protection against lung cancer. We will engage in a collaborative effort to use relevant mouse models of cancer to determine the best combinatorial approaches incorporating the activity of drugs inducing immunogenic cell death with immune modulatory antibodies.

The impact of such therapies will be tested in preclinical models of lung cancer alone and in combination with chemo, radio and immune modulatory agents in order to inform future design and implementation of clinical trials harnessing the immune response.

Through a multidisciplinary approach incorporating preclinical and clinical research, we will establish a strong, continually growing and successful translational cancer immunology programme for the treatment of lung cancer.

“The multidisciplinary expertise within Manchester and UCL will drive development of even more effective immunotherapies that target not just the tumour cell but also the tumour microenvironment and the immune system.”
The CRUK Drug Discovery Unit (DDU) at Manchester was established in 2009 following a strategic decision to increase small molecule drug discovery alongside the CRUK core funded research institutes in Manchester and Glasgow. We have opened and equipped a new laboratory and recruited a team of 28 biologists and medicinal chemists with a mixture of academic and industrial experience.

The laboratory is underpinned by state-of-the-art bio- and chemo-informatics platforms for drug discovery. The CRUK Manchester Institute is a centre of excellence for basic and translational cancer research and has provided an ideal environment for cancer drug discovery focused on unmet patient needs. Over 40% of the novel targets that the DDU have progressed have potential for use in lung cancer. The new CRUK Lung Cancer Centre of Excellence at Manchester and UCL will greatly enhance our interface with cutting edge research in lung cancer.

The Drug Discovery Unit team has been assembled from drug discovery scientists with an impressive track record of success having been involved in the delivery of over 50 clinical development candidates, 35 of which have progressed to clinical trials and 2, so far, to full registration. The proximity to basic, translational and clinical research expertise has proved invaluable in the selection and validation of novel cancer drug discovery targets. One particularly successful approach during
the last four years has been the provision of quality small molecule tools to local researchers for target validation studies. The DDU is also outward facing beyond Manchester and, as well as working with other CRUK Principal Investigators in the UK, we have secured several valuable collaborations with international Pharmaceutical companies – AstraZeneca and GSK – and Biotech companies to progress our projects. Most importantly, we have now built a robust drug discovery portfolio and have progressed two of these projects to the advanced, lead optimisation stage. Both of these targets have potential for therapeutic use in lung cancer.

Our ambition is to deliver preclinical drug candidate molecules for progression into the clinic. Given the historically high rates of drug discovery project attrition, we need to identify new targets and look forward to attracting more lung cancer drug target opportunities from the CRUK Lung Cancer Centre of Excellence at Manchester and UCL.

“Our Drug Discovery Unit will translate basic science discoveries into novel preclinical candidate drug molecules that can be tested in the clinic.”
EARLY DETECTION AND PRE-INVASIVE DISEASE

Dr Richard Booton
Head of the Lung Cancer Early Detection group in the Institute of Cancer Sciences at The University of Manchester and Consultant at University Hospital of South Manchester NHS Foundation Trust

Professor Sam Janes
Chair in Respiratory Medicine at UCL and Consultant at University College London Hospitals NHS Foundation Trust

Compared with other common malignancies, the prognosis for lung cancer patients is poor, with more than 75% of patients presenting with largely incurable advanced stage lung cancer. A new strategy is needed, aimed at detecting lung cancer earlier, treating in a lung sparing manner and preventing early disease by understanding pre-cancerous lesion development.

Understanding more about the key steps in early lung cancer pathogenesis will allow the development of novel therapies targeting early pre-invasive disease. This could possibly lead to chemo-prophylactic therapies in those most at risk.

Our research targets include screening or surveillance of asymptomatic high risk patients and detecting and biologically interrogating pre-invasive lung cancer lesions to enable mechanism directed chemoprevention. We also aim to better understand the clonal origins and tumour evolution of early lung cancer to deliver effective lung sparing treatments for pre-invasive (and very early invasive) disease, and to develop quality assured management pathways for suspected disease that facilitate rapid diagnosis. Finally, identifying patients at highest risk of disease recurrence post-radical treatment and establishing a cross site quality assured tissue bank to support personalised and precision medicine will be vital.

Manchester and UCL already share clinical expertise in early lung cancer detection and treatment; with shared protocols for patient follow up, treatment and research biobanking across both institutions. The new CRUK Lung Cancer Centre of Excellence at Manchester and UCL will expand the previously established University College London Hospitals NHS Foundation Trust (UCLH) Lung Surveillance study that has led to an unsurpassed collection of patients studied longitudinally, with lesion, blood and sputum samples collected from the same patients and lesions over time, enabling genetic mapping of lesion progression or regression.
Together we lead the CRUK funded LUNG-SEARCH study investigating the use of sputum, auto fluorescence bronchoscopy and CT in the early detection of lung cancer in high risk populations. UCL was recently awarded funding to examine the feasibility of CT screening in a UK population of lower socioeconomic status. Manchester and UCL already collaborate on several rapid diagnosis and staging studies and are co-applicants on the PEARL trial – an early intervention study on pre-invasive disease. UCLH also leads the STREAMLINE whole body MRI diagnosis and staging trial. We have a critical mass of over 20 clinicians and scientists working on early lung cancer pathogenesis and investigating the role of stem cells in tumour initiation and treatment.

We will develop the largest collection of samples from high risk individuals with pre-cancerous lesions enabling the clinical and biological delineation of the evolution of squamous cell cancer. In collaboration with the Sanger Institute in Cambridge, a large scale whole genome sequencing programme will be undertaken to examine the key genetic features that lead to progression of pre-cancerous lesions. Exome sequencing will be combined with methylation and gene expression arrays to distinguish the genetic and biological markers of lesion progression compared to those lesions that regress. Mechanistic investigation of key genes that predict progression will be examined with a view to determining biomarkers of progression/risk, candidates for circulating biomarkers of lung cancer risk/detection and the development of novel therapies targeting early lung cancer development.

“We with more than 75% of patients presenting with largely incurable advanced stage lung cancer, we aim to develop new tools for early detection of pre-invasive disease to improve patient survival.”
TUMOUR EVOLUTION
AND HETEROGENEITY

Modern technologies are increasingly revealing the tremendous diversity between cancers from different patients, despite similar characteristics under the microscope in the pathology department. Furthermore, in depth analysis of tumours from individual patients is increasingly revealing the diversity of genetic changes both within and between biopsies from the same tumour.

Such diversity both between and within individual tumours presents difficulties for the modern era of personalised medicine and the development of new drugs. Of even greater concern is emerging evidence that tumours with greater diversity have worse clinical outcome and an increased propensity for resistance to common anticancer treatments.

The Tumour Evolution and Heterogeneity theme is supported by a dedicated lung cancer next generation sequencing facility and a Good Clinical Practice (GCP) laboratory. We work on target validation and patient stratification within therapeutic trials aimed at understanding the changing landscape of the lung cancer genome in individual patients over time and exploiting such changes for therapeutic benefit. Between the CRUK Manchester Institute and University College London, we have access to world class computing infrastructure and data storage. Our bioinformatics teams in London and Manchester are developing new tools to decipher the evolution over time of both non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) genomes. In parallel, utilising high resolution microscopy, RNA interference and CRISPR genome editing technologies, we are endeavouring to explore the functional basis of somatic changes identified within individual cancer genomes, prioritised through bioinformatics analyses. The Centre has close links with industry and is developing a series of cancer clinical trials aimed at identifying key drivers of drug resistance in lung cancer and targeting tumours optimally, based on an understanding of the evolution of individual lung cancer genomes. We will focus on the changing dynamics of cancer cell diversity.
during anticancer treatment to develop improved understanding of the mechanistic basis for drug resistance and treatment failure. The Centre will study the mechanical processes within a cancer cell that lead to differences between tumour cells and the ability of a cancer cell to tolerate ongoing changes to its genetic material.

TRACERx (TRACking Cancer Evolution through therapy/Rx), the lung cancer evolution longitudinal patient cohort study, will form a central component of studies focussed on tumour evolution and intratumour heterogeneity. The DARWIN (Deciphering Antitumour Response With Intratumour Heterogeneity) clinical trial programme will provide the clinical basis to explore the impact of tumour subclonal dynamics on drug response, acquisition of resistance to therapy and clinical outcome and develop sustainable links with pharmaceutical partners. Through a greater understanding of the processes that drive tumour cell diversity, the Centre will develop means to target diversity through pharmacologic intervention. Through the infrastructure developed, the Centre will provide the pharmaceutical industry and academic clinicians with a personalised therapeutic service enabling the evolution and adaptation of tumours from clinical trial patient cohorts to be studied in real time. Ultimately, it is hoped that such developments will improve precision cancer medicine approaches and the clinical outcome for patients suffering from lung cancer.

“Our collaborative multidisciplinary approach is essential to better understand tumour diversity so that new strategies that overcome cancer cells’ ability to evolve and thereby evade treatment can be developed.”
BIOMARKERS

Successful delivery of precision medicine to lung cancer patients depends on robust biomarkers to define prognosis, determine optimal dose and select patients most likely to benefit. Our Centre has considerable strengths in biomarker science with strong research programmes in tissue, circulating and imaging biomarkers.

Clear synergies exist between the Biomarkers and Tumour Heterogeneity and Evolution themes where our biomarker expertise is being deployed within the pioneering TRACERx protocol. Biomarker candidates emanating from our Basic Science and Immunology themes will be developed, validated and qualified via innovative clinical trials led from within the Centre.

Our Centre has one of the largest biomarker hubs in the UK run to Good Clinical Practice (GCP), where biomarker data can be used for clinical decision making according to EU regulations for clinical trials. Acknowledging challenges associated with serial lung biopsy, we have developed an extensive portfolio of circulating biomarker assays. These include the enumeration and molecular characterisation of circulating tumour cells (CTCs), sensitive multiplex ELISA panels for angiogenesis and cell death biomarkers and a comprehensive ‘tool kit’ of approaches to assess circulating nucleic acids (cfDNA and miRNA). CTC profiling using advanced bioinformatics algorithms for single cell analysis will be used to evaluate heterogeneity and discover biomarkers. In parallel, we established unique small cell lung cancer (SCLC) patient CTC derived mouse models – termed CDX – generated at patient presentation and/or at relapse. Our new SCLC mouse models now afford
unparalleled opportunity to explore disease biology, interrogate mechanisms of drug resistance, test novel therapeutics (integrating with other Centre themes) and develop tissue, circulating and imaging biomarkers for this disease for which as yet no targeted therapies have made an impact.

Lung cancer imaging is a major focus within our two aligned CRUK/EPSRC Imaging Centres. Establishing imaging tools to probe the molecular basis of cell-to-cell intra-tumour heterogeneity to complement our genomic studies represents a major step forward and is a goal of the Biomarkers theme. Focussed on druggable receptor tyrosine kinases (e.g. EGFR, c-Met) and associated signalling networks, we are developing advanced biophysical techniques to measure protein-protein interactions (from the less than 10nm through to 200nm separation range by a combination of FLIM histology and superresolution) in tumour biopsies and CTCs from patients pre and post treatment with these targeted therapies. We aim to detect onset of signal transduction ‘rewiring’ processes early such that intervention can occur before drug resistance is fully developed. Tissue imaging based pathway analyses will be coupled to in vivo PET and multi-parametric MR imaging, underpinned by the development of new PET/SPECT tracers, for example against c-Met, that are being developed with our Cancer Research UK/EPSRC Cancer Imaging Centres. We were the first to publish methods for motion corrected DCE-MRI applied to lung imaging, we are leading development of Oxygen Enhanced MRI for imaging the lung and we are exploring the relationships between Diffusion Weighted MRI and drug induced cell death.

In summary, the Biomarkers theme will integrate the basic and clinical research within our centre as we strive to improve patient outcomes with hypothesis driven, biomarker guided clinical trials.

“Our strengths in biomarker research will facilitate successful delivery of precision medicine for lung cancer patients by providing robust biomarkers that define prognosis, determine optimal dose and select patients most likely to benefit from specific treatments.”
Clinical trials are central to the introduction of novel treatments into the clinic and the development of better, more effective, standards of care. From a disease once deemed insensitive to chemotherapy, there now exist gold standard treatment regimens for the therapeutic management of lung cancer. With the central objective of improving patient outcomes, we aim to design and perform internationally competitive and practice changing clinical trials in lung cancer.

Manchester and UCL have been world leading in the conduct of seminal clinical trials. A pioneering study of gemcitabine and platinum helped establish the regimen as the standard first line treatment of advanced non-small cell lung cancer (NSCLC) in Europe. At the turn of the century, Manchester treated the first ever NSCLC patient with gefitinib, paving the way for a new era of personalised treatments in this disease, and UCL recently conducted the ET trial, the largest randomised prospective biomarker study of patients with advanced NSCLC.

Capitalising on a uniquely diverse large patient population,
Manchester and UCL both have well established Clinical Trials Units (CTUs) enabling us to drive research and establish large collaborative multicentre trials of the highest scientific excellence. The Christie in Manchester houses the largest early phase treatment unit in the world, with around 400 trials taking place at any one time, and UCL has one of the largest CTUs in the UK, developing and conducting small and large scale trials in lung cancer since 1978.

With the establishment of the Centre, we have an exciting opportunity to further implement biomarker driven early phase studies and continue to investigate the combination of radiotherapy, chemotherapy and targeted therapies in lung cancer. These studies will draw on expertise across all research themes within the Centre and will involve two-way interaction between the laboratory and the clinic. Through our clinical and translational research programme, we aim to bring in the best new treatments for our patients through practice changing phase III trials.

“Manchester and UCL have a strong heritage in clinical trials, which underpin the bench to bedside delivery of innovative treatments that improve outcomes for lung cancer patients.”
Radiotherapy plays an important role in the management of lung cancer, with over 50% of patients receiving this treatment modality at some point during their treatment. The Christie NHS Foundation Trust provides the largest radiotherapy service in the country – with around 600 lung cancer patients treated with radical radiotherapy a year – and, together with University College London Hospitals NHS Foundation Trust (UCLH), aims to form a cohesive and collaborative clinical and translational research group.

The core principle of the group is to provide individualised radiotherapy treatment that continually pushes treatment boundaries and thus leads to improved outcomes for lung cancer patients. Our research is underpinned by state-of-the-art radiotherapy delivered routinely to our patients including 4DCT and FDG PET-CT planning, intensity modulated radiotherapy, including stereotactic radiotherapy, and online cone beam CT verification.

Radiotherapy research in lung cancer is multidisciplinary and benefits from expertise in several disciplines within the field of oncology including clinical oncology, medical oncology, imaging, medical physics, radiobiology, circulating biomarkers, proteomics and immunotherapy. This unique combination of expertise and experience has led to the development of the only biomarker programme in the UK that aims to predict response and toxicity in lung cancer patients treated with radical radiotherapy. The Radiotherapy departments and Clinical Trials Units at The Christie and UCLH have developed strong collaborative links, enabling early phase trials combining thoracic radiotherapy and mechanism based therapies. There is also specific expertise and leadership in the multimodality treatments for stage III non-small cell lung cancer (NSCLC) (MEKRT and isotoxic IMRT trials), limited disease small cell lung cancer (SCLC) (CONVERT trial), stereotactic radiotherapy for early stage NSCLC (lungTech trial) and radiotherapy for mesothelioma (PIT trial). In addition, Manchester and London will host the UK’s only two high energy Proton Beam Therapy Centres, with unique
opportunities to codevelop joint radiation clinical research for patients, including trials in locally advanced lung cancer and mesothelioma.

Our main aim is to position the Centre as an international leader in the field of lung cancer radiotherapy, working collaboratively within the areas of personalised therapy, theragnostics, combined therapies and proton therapy. The delivery of personalised, highly technical radiotherapy, including the evolution of the radiotherapy pathway, should increase accuracy and precision of treatments delivered. This involves interaction and facilitation with multidisciplinary research groups. Theragnostics – predictive models of radiotherapy response and toxicity including biomarkers based on population data – will also enable more individualised treatments. The advancement of early phase trials of combined radiotherapy will include novel agents such as immunotherapy. We will engage and collaborate on phase II/III radiotherapy trials to impact standard of care and explore the role of proton therapy in lung cancer and mesothelioma as an active member of the National Cancer Research Institute Clinical and Translational Radiotherapy (CTRad) Proton Beam Therapy Research Group.

“Radiotherapy continues to be the backbone of many lung cancer treatment regimens and practice-changing trials to optimise delivery to individual patients are key to improving patient outcomes.”
INTERDISCIPLINARY RESEARCH
INTERDISCIPLINARY RESEARCH

The strength of the CRUK Lung Cancer Centre of Excellence at Manchester and UCL will be the interaction of scientists within different research themes at both institutions, allowing us to expand our research interests into innovative and exciting new areas of lung cancer research.

One such project that already draws on the strengths and expertise of a number of the Centre’s research themes is TRACERx – TRAcking Cancer Evolution through therapy (Rx). The trial brings together teams from across the Basic Science, Biomarkers, Tumour Evolution and Clinical Trials research themes at both Manchester and UCL.
TRACERx

The TRACERx – TRAcking Cancer Evolution through therapy (Rx) – study was launched in July 2013 by Cancer Research UK. This £14 million study spanning nine years aims to investigate how lung tumours evolve over time as patients receive treatment. Bringing together researchers from Manchester and UCL alongside a national network of research and clinical trials centres, it will recruit 850 lung cancer patients from across the UK.

TRACERx focuses on the genomic analysis of early stage non-small cell lung cancer (NSCLC) and its changing nature over time. Patients with primary NSCLC, suitable for surgical resection with curative intent, will be potentially eligible for TRACERx. Each patient consenting to the program will donate their tumour tissue, resected during the course of surgery, for high depth tumour sequencing of multiple sites of the disease. If the disease recurs, further consent will be requested to analyse tumour tissue from the recurrent site of disease to establish how the tumour has changed over time.

Various analyses are carried out on each sample in order to assess genetic intra-tumour heterogeneity and its evolution from diagnosis through the disease course. These analyses include both molecular pathology and next generation sequencing approaches to decipher tumour genetic driver events that might be targetable within the DARWIN program or other trials within the Centre. Whole exome sequencing – detection of somatic point mutations, insertions, deletions and structural changes in the tumour genome – will allow the construction of a phylogenetic tree of the tumour regions and lead to a greater understanding of the origins of the lethal subclone that results in the development of metastatic disease. This aspect of the study builds on work at UCL that has explored tumour evolution in both lung and renal cancers and shown that cancer subclones are spatially diverse.

Patients also have blood samples taken at each time point, to allow the assessment of circulating tumour cells (CTCs) and fragments of tumour genetic material, such as circulating free tumour DNA (cfDNA). Researchers are exploring whether genetic mutations can be detected in CTCs and cfDNA – allowing the investigation of tumour heterogeneity in a minimally invasive manner.

Clinical and genomic data is integrated to permit comparison between indices of intra-tumour heterogeneity and drug resistance and clinical outcome. The amount of data produced by the study – up to ~6 petabytes – offers the opportunity to build an advanced cancer bioinformatics infrastructure, linked with clinical trial implementation, across the country and develop national cancer sequencing expertise.
TRAINING
Training the next generation of scientists is at the heart of the CRUK Lung Cancer Centre of Excellence at Manchester and UCL. The Centre provides a comprehensive PhD postgraduate training programme, with a strong focus on lung cancer molecular biology, to develop clinical and non-clinical academics of the future.

The training programme covers a range of different technologies, providing a substantial competitive advantage for obtaining positions at the next career level. Through the Manchester/UCL Clinical Research Training Fellowship scheme, graduate students with clinical backgrounds will be encouraged to pursue research in lung cancer related programmes.

The partnership enables us to offer challenging and stimulating projects in a wide range of lung cancer related research areas. Our unrivalled expertise and facilities present the opportunity to work closely with world leading research scientists and clinicians, whilst having access to state-of-the-art laboratories.

Each PhD student will have the opportunity to undertake core training at both Manchester and UCL sites where joint supervision ensures a supportive environment that encourages students to flourish as they move towards becoming independent researchers.

An active seminar series and a wide range of skills and development courses encourage intellectual and social interaction between students. The annual CRUK Lung Cancer Centre of Excellence Workshop also provides PhD students, clinical fellows and postdoctoral scientists with the opportunity to hear about world leading lung cancer research, formally present their work and receive constructive feedback from senior colleagues and internationally renowned leaders in the field.
EXPLOITING BIOMARKER EXPERTISE TO ELUCIDATE MECHANISMS OF RESISTANCE

I am in the third year of my PhD project investigating acquired resistance to chemotherapy in small cell lung cancer (SCLC) through the analysis of circulating biomarkers in Professor Caroline Dive’s research group at the CRUK Manchester Institute. SCLC has a high response rate to first line chemotherapy but unfortunately the cancer rapidly progresses and is usually resistant to further chemotherapy.

Utilising circulating tumour cells (CTCs) isolated from the blood of patients prior to receiving chemotherapy and again following the development of relapsed disease, I am exploring the changes that potentially lead to disease resistance. I am using data generated from both conventional sequencing and next generation sequencing of amplified DNA from single CTCs to interrogate mutational hotspots, whole exome changes and chromosomal aberrations in SCLC. The goal of this work is to identify potential mechanisms of resistance that could provide new drug targets, with the aim of improving patient outcomes. My studies on isolated CTCs dovetail with the group’s recent development of SCLC CTC derived mouse models where mechanisms underpinning drug resistance can be investigated at the functional level.

“During a PhD it’s important to become a specialist in your specific area, but there’s always a danger of getting tunnel vision. Being able to meet researchers from across the Centre will give me a fresh perspective on my project. I’m really excited about working with scientists from different laboratories and perhaps even setting up future research collaborations.”

Louise Carter
Clinical Fellow, CRUK Manchester Institute
REVEALING GENETIC DIFFERENCES THAT IMPACT PATIENT OUTCOMES

“As someone who is involved in a big multicentre trial, it’s the collaborative nature of the Centre that most appeals to me. The fact that all the research themes interact with each other will allow me to study lung cancer from every angle.”

Mariam Jamal-Hanjani
Clinical Fellow, UCL Cancer Institute

I completed my undergraduate training in Physics at UCL and went on to study Medicine, graduating in 2005. During my training as a specialist registrar in Medical Oncology, I was awarded a Cancer Research UK Clinical Research Training Fellowship for a PhD and am currently working in Professor Charles Swanton’s laboratory at the UCL Cancer Institute.

My research project involves studying intratumour heterogeneity and characterising the genomic aberrations in non-small cell lung cancer (NSCLC) by sequencing multiple tumour regions collected from primary lung tumours in patients eligible for resective surgery. This project follows on from existing work in Professor Swanton’s laboratory, which is beginning to reveal the complexity of NSCLC evolution and intratumour diversity. My project also involves determining whether the genomic aberrations, identified using multi-region sequencing, can be detected in circulating-free tumour DNA (cfDNA) in blood samples collected from patients, and whether clonal as well as subclonal mutations can be identified so that cfDNA may be used for the detection of intratumour heterogeneity - offering a minimally invasive method to monitor NSCLC throughout the disease course.

In order to understand the impact of tumour clonal heterogeneity upon therapeutic outcome and how cancer subclones compete and adapt during tumour evolution, I have been involved in the development of the multi-national centre study TRACERx (TRAcking Cancer Evolution through therapy (Rx)).
The CRUK Lung Cancer Centre of Excellence partners offer some of the best infrastructure and facilities in the UK for supporting basic, translational, clinical and imaging research into lung cancer. The wealth of cutting edge laboratories and clinical facilities enables pioneering studies into novel approaches to the detection, monitoring and treatment of the disease and the development of personalised medicine.

Laboratory studies are supported by state-of-the-art equipment and core facilities. Examination of the genetic drivers and molecular processes underpinning lung cancer development can be explored using a variety of methods. Just as two examples, UCL is home to an extensive RNAi library, allowing researchers to explore the effects of individual genes in both mouse and human cancer cells, and at the CRUK Manchester Institute, a gatedSTED microscope enables scientists to visualise cancer at the molecular level.

Expansion of fundamental research into cancer cell biology is being brought about through ambitious investment. In Manchester, the iconic new Manchester Cancer Research Centre building is due to open at the end of 2014, providing additional space for around 150 University researchers and 100 of The Christie’s research and development support staff.

Translation of laboratory findings into clinical benefit for patients is vital for improving outcomes and the CRUK Drug Discovery Unit (DDU) in Manchester is well equipped to focus on producing novel anticancer agents. Bringing together biologists and chemists,
the DDU takes molecular targets identified by groups looking at cancer cell biology and, through screening libraries, computer aided design and experimental optimisation, aims to develop new medications.

Biobanking allows our researchers to easily access large numbers of high quality biological samples from cancer patients. Infrastructure for biobanking exists at Manchester and UCL to enable coordination of sample collection and to integrate clinical partners with laboratory based users. The UCL/UCLH Biobank stores a range of normal and pathological specimens surplus to diagnostic requirements, whilst the MCRC Biobank collects a sample ‘six pack’ – fresh frozen diseased and normal tissue, formalin fixed diseased and normal tissue and pre-operative blood and urine samples – from all consenting patients during surgery specifically for research purposes. Biobanking of circulating nucleic acids and isolated circulating tumour cells (CTCs) is also now routine pre and post therapy within the MCRC. Both Biobanks have been awarded ethical approval as Research Tissue Banks and have a standardised consent procedure, which allows long term storage of samples for future projects and the use of samples in a wide variety of studies and experiments.

Extensive imaging facilities are available at Manchester and UCL. In Manchester, the Wolfson Molecular Imaging Centre offers PET and MR imaging, including two research dedicated clinical PET scanners, two preclinical PET cameras, a cyclotron, radiochemistry production facilities, analytical and bioanalysis laboratories and a 1.5T research MRI scanner. Elsewhere, there are two 3.0T clinical research MRI scanners and preclinical MRI equipment. In London, the recently opened UCLH Macmillan Cancer Centre contains the UK’s first simultaneous PET-MR scanner and across the UCL campus are major centres with other advanced clinical and preclinical scanners carrying out research into advanced biomedical imaging and medical image computing.

Capitalising on a uniquely diverse large patient population, Manchester and UCL have well established Clinical Trials Units (CTUs) providing a supportive, patient focussed environment to host clinical research of the highest scientific excellence. The Christie in Manchester houses the largest early phase CTU in the world, with around 400 trials taking place at any one time, and UCL has one of the largest CTUs in the UK, leading practice changing trials in lung cancer since 1978.

The Christie is also home to one of the world’s largest radiotherapy units, carrying out over 80,000 treatments every year. From 2018, UCLH and The Christie will become the first centres in the UK to offer Proton Beam Therapy, following a £250 million investment by UK government. This advanced form of radiotherapy spares much more of the surrounding healthy tissue and is particularly useful for deep lying tumours. The development of the new Proton Beam Therapy centres offers the opportunity for existing and newly recruited research expertise in radiotherapy, medical physics and particle physics within Manchester and UCL to be harnessed to investigate and improve this cutting edge treatment.
PARTNERS
PARTNERS DRIVING PROGRESS

The CRUK Lung Cancer Centre of Excellence at Manchester and UCL incorporates expertise from a number of different organisations, including The University of Manchester, Cancer Research UK Manchester Institute, The Christie NHS Foundation Trust, University Hospital of South Manchester NHS Foundation Trust, Manchester Cancer Research Centre, UCL Cancer Institute, UCLH Macmillan Cancer Centre and UCLPartners.

The University of Manchester
A member of the Russell Group, The University of Manchester is one of the largest universities in the UK. According to the results of the 2008 Research Assessment Exercise, the University is officially ranked best in the UK for cancer research. There are two hubs for cancer research within the University: the Faculty of Life Sciences – home to the Molecular Cancer Group – and the Faculty of Medical and Human Sciences, which encompasses the Institute of Cancer Sciences and the Manchester Pharmacy School as well as groups with expertise in cancer imaging and stem cell research.

Cancer Research UK Manchester Institute
The Cancer Research UK Manchester Institute is a research institute within The University of Manchester, and is one of five research institutes core funded by Cancer Research UK. Research at the Institute spans the whole spectrum of cancer research, from programmes investigating the molecular and cellular basis of cancer to those focused on translational research and the development of novel therapeutic approaches.

The Christie NHS Foundation Trust
The Christie specialises in cancer treatment, research and education, and is the largest cancer centre in Europe. As well as treating 40,000 patients a year from across the UK, its experts have been pioneering cancer research breakthroughs for more than 100 years. The Christie serves a population of 3.2 million people across Greater Manchester and Cheshire, with 26% of patients referred from across the UK. Based in Manchester with radiotherapy centres in Oldham and Salford, The Christie is known for many world firsts, which have impacted cancer treatment on a global scale and it became the first UK centre to be officially accredited as a comprehensive cancer centre.

University Hospital of South Manchester NHS Foundation Trust
University Hospital of South Manchester is a major acute teaching hospital trust providing services for adults and children and community services that were formerly operated by Manchester Primary Care Trust. The trust is home to the North West Lung Centre, which has an international reputation for respiratory medicine and offers specialist lung cancer services.

Manchester Cancer Research Centre
The Manchester Cancer Research Centre was formed in 2006 by The University of Manchester, Cancer Research UK and The Christie NHS Foundation Trust. It has since been established as the cancer research arm of the Manchester Academic Health Science Centre, which is a strategic partnership between the University and six NHS Trusts across Greater Manchester.

The MCRC coordinates basic, translational and clinical cancer research across its partner organisations. The Centre is also home to the MCRC Biobank, which has been set up to collect human samples from cancer patients across Greater Manchester, and the Manchester Experimental Cancer Medicine Centre.
UCL Cancer Institute
The UCL Cancer Institute was established in 2007 and is the hub for cancer research at University College London – it hosts the majority of cancer research scientists and acts as the nucleus for the UCL Cancer Research UK Centre and the UCL Experimental Cancer Medicine Centre. Particular areas of strength within the Institute include stem cell biology, immunology and immunotherapy, drug development, viral oncology and genomics and bioinformatics.

UCLH Macmillan Cancer Centre
The purpose built UCLH Macmillan Cancer Centre provides specialist cancer treatment to University College London Hospitals. Based at the Centre are outpatient and day care cancer services and a dedicated teenage and young adult cancer service, as well as state-of-the-art imaging equipment, including the UK’s first PET-MR scanner. The Centre is located across the road from the UCL Cancer Institute and enables the expansion of patient orientated and translational cancer research.

UCLPartners
An academic health science partnership between higher education and NHS organisations, UCLPartners was established in 2009. It has since expanded and now covers north east and north central London as well as parts of Hertfordshire, Bedfordshire and Essex. Serving a population of six million people, UCLPartners brings together 100,000 health professionals and academics in order to translate cutting edge research and innovation into measurable health gain for patients in London and across the UK.
The management of the Cancer Research UK Lung Cancer Centre of Excellence at Manchester and UCL and the implementation of its strategy are supported by a number of boards and committees:

**Cancer Research UK Scientific Executive Board**
- The External Scientific Advisory Board (ESAB) is an independent body carrying representation from international senior academics, clinicians and patient representative groups. Meeting annually, the Board is tasked with advising the CRUK Lung Cancer Centre of Excellence leads on the scientific strategy of the Centre and its implementation.

**Centre Management Group**
- The Centre Management Group is charged with leading the development and delivery of the agreed research strategy for the CRUK Lung Cancer Centre of Excellence at Manchester and UCL, as well as overseeing the governance, resource and financial arrangements of the Centre.
- The Group manages the Centre on a day to day basis, as well as coordinating and regularly reviewing the progress and success of the Centre’s research themes.

**External Scientific Advisory Board**
- The committee actively manages the research themes, facilitating ongoing and coherent integration of projects to add value, as well as providing an internal peer review process for the Centre’s grant applications.
- The committee also oversees and identifies areas of potential collaboration both within and outside the Centre.

**Research Programme Management Committee**
- The Research Programme Management Committee is responsible for developing and implementing the programme of work undertaken at the CRUK Lung Cancer Centre of Excellence and overseeing the Centre’s training programme.