Contents

Message from Professor Gillies McKenna, Head of Department 2

Introduction 3

DNA Damage and Repair 4

Tumour Microenvironment 16

Clinical and Translational Research 28

Scientific Cores and Specialist Facilities 50

Training 60

Communicating the Impact of Research 62

Working in Partnership 64

Running the Department 66

Acknowledgements

With thanks to:
Photography by KJG Photography and Andrew Ogilvy
Design by The Image Works UK Ltd
Project managers: Claire Shingler and Peter O’Neill
Writers/editors: Claire Shingler, Peter O’Neill,
Martin Christieb, Sarah Norman, Pam Nieto
Other images supplied by research Group Leaders and Scientific Core Leaders

For more information about our research and details of publications, please go to www.oncology.ox.ac.uk
In 2010, the Department of Oncology was formed with the vision of enhancing basic and clinical cancer research in Oxford. This was to be underpinned by maximising opportunities for multidisciplinary collaboration and scientific interaction with the ultimate goal of increasing cancer cure rates.

As Head of the Department of Oncology, it is with great pleasure that I can report that we are achieving this vision and fulfilling our aim to facilitate rapid translation from scientific discovery to patient benefit. Together with the Cancer Research UK and Medical Research Council Oxford Institute for Radiation Oncology, we have focused our efforts on better understanding DNA damage and repair processes, defining the tumour microenvironment and enhancing radiotherapy treatments.

To realise success, it is vital that our research comes from a range of disciplines – some at the heart of traditional cancer research and others not historically linked with cancer. With this at the forefront of our minds, we have invested heavily in key areas, such as medical physics, imaging, bioinformatics, pathology and clinical trials, to expand our capabilities in those areas where multidisciplinary collaboration is the only way to excel and lead the field. In Oxford, we are in a unique and privileged position to have a great wealth of broad-ranging expertise and a powerful network of cancer researchers.

We have worked hard to form close and lasting partnerships across Oxford. Thanks to a series of major initiatives managed through the Department, such as the CRUK Oxford Centre, the CRUK & EPSRC Oxford Imaging Centre, the Biomedical Research Centre Cancer Theme and the Experimental Cancer Medicine Centre, we have seen major developments in our understanding of cancer. There have been huge advances, to name but a few, in determining potential molecular agents to improve efficacy of treatment, in applying imaging methods for earlier detection of metastases and identifying biomarkers to aid in defining the most appropriate treatment for each patient. By coupling these partnerships to effective collaboration with colleagues in the Oxford University Hospitals NHS Trust, we strive to become the leading centre for translational early phase oncology trials in the UK and to lead national networks in our areas of expertise such as radiotherapy and precision medicine.

We pride ourselves on supporting and training the next generation of world leaders in cancer research to ensure our research and clinical excellence continues over the long term. Our multidisciplinary graduate and postdoctoral training programmes for both scientists and clinicians are internationally recognised and attract the most promising and able researchers.

Our main research themes of DNA damage and repair, cell death and repair processes, defining the tumour microenvironment and enhancing radiotherapy treatments are working towards gaining a Silver award.

In recognition of our efforts, we were awarded a departmental Athena SWAN Bronze award in July 2014 and are working hard to ensure that our most talented researchers, both men and women, are supported to become the future leaders in their fields. We have embedded into our culture an annual personal development review process for all staff and we provide a comprehensive portfolio of personal and professional skills development.

Our main research themes of DNA damage and repair, tumour microenvironment and clinical and translational research are strongly supported by an expanding group of core specialist facilities equipped with state-of-the-art equipment and staffed by highly qualified individuals with knowledge and expertise in a number of areas. We have strong links with other parts of the University and also benefit from local expertise in neighbouring University facilities such as the Target Discovery Institute.

All research and clinical activities are underpinned by a multi-faceted administration team who provide financial and HR management, graduate studies support and facilities and Health and Safety provision.

Our research and clinical activities contribute to an annual Department turnover of £26M. Much of this is external research funding, including over £10M per year provided by CRUK and the MRC as funding to the CRUK/MRC Oxford Institute for Radiation Oncology, a specialist radiation biology centre of excellence which sits within the Department. Other funding comes from a variety of sources, including charities, industry, government (NIHR, Department of Health and Research Councils) and the European Commission (EC). The department is involved in numerous clinical trials to take our research to patients.

For more information about our research and details of publications, please go to www.oncology.ox.ac.uk
DNA Damage and Repair

DNA contains the critical genetic information in all living cells. When cells grow and divide they need to correctly replicate their DNA and repair any mistakes or damage to their DNA. Unrepaired damage can lead to accumulation of mutations, in turn producing genome instability which can ultimately drive the uncontrolled proliferation of cells that is one of the hallmarks of cancer.

DNA damage responses

We are particularly interested in characterising the mechanisms of induction of damage to DNA and understanding how the damage is repaired. The research focuses on identifying biomarkers in DNA damage and repair pathways for clinical application; identifying targets in these repair pathways that could be exploited for therapeutic gain; and taking compounds active on these targets to clinical trial.

Genomic stability is essential for cells to survive and to prevent the onset of tumourigenesis. DNA damage responses, mediated by signalling networks, play a key role in maintaining genomic stability and are affected by several cellular processes such as cell cycle progression and replication, and by chromosome structure, chromatin and telomeres. Failure of these responses causes genomic instability and cancer.

Research at Oxford brings together scientists working on different but complementary elements that impact on DNA damage responses; these range from studies on telomeres and maintenance of telomere integrity, to chromosome structure and the mechanisms of DNA damage repair. A diversity of approaches and expertise is harnessed using simple organisms such as yeast, through to human cell culture and mouse models to provide new insights into the maintenance of genomic stability and its role in preventing cancer development and progression.

DNA damage and repair as a therapeutic target

DNA damage and repair plays a dual role in cancer: aberrant repair drives genomic instability and tumourigenesis. However, many therapeutic agents and radiation exert their anticancer effects by generating DNA damage. For example, radiotherapy and some chemotherapies cause single- and double-strand breaks, DNA interstrand cross links (ICLs—a particularly toxic form of DNA damage), replication lesions and base damage. These all prevent cancer cell replication and drive cancer cell death. Thus, repair of this ‘therapeutic’ damage can make cancer cells insensitive to these agents.

Researchers in Oxford are identifying and characterising key molecules and mediators in DNA damage and repair pathways that play a pivotal role in determining cancer cell sensitivity to DNA damage-inducing agents. The aim is to develop novel techniques for sensitising (or re-sensitising) cancer cells to DNA-damaging radiotherapy or chemotherapy in order to enhance tumour cell eradication while reducing damage to non-cancerous tissue.

DNA damage in early detection of cancer

Oxford researchers are using several biomarkers, which are proving to be a valuable research tool, to identify cells with DNA damage accumulation and detect cells which ‘poorly’ repair DNA damage. Identification of cells with DNA damage accumulation would also be a valuable clinical tool for early detection of potentially cancerous cells. These approaches are also being used for early detection of DNA damage in model systems.

The research in Oxford on DNA damage and repair mechanisms is providing new insight into the aberrant processes and key mediators that drive cancer development and progression. This insight will facilitate the identification of novel targets for therapeutic intervention. It will also contribute to improvements in the effectiveness of therapies that work by introducing DNA damage in cancer cells.
**Nucleic Acids Research Group**

Our group designs and synthesises chemically modified DNA for diagnostic and therapeutic applications.

My research is in nucleic acid chemistry and structure, and the application of nucleic acids and analogues to diagnostics and therapeutics. Using various biophysical techniques including X-ray crystallography we study the nature of base mispairing in DNA, the structure of DNA duplexes containing mutagenic lesions and the interaction of DNA with specific repair enzymes. We have also developed rapid methods for the identification of mutations in the human genome without the need for DNA sequencing. The best example is Scorpion primers which are used in fluorogenic real-time PCR to analyse genomic DNA sequences at specific loci. Scorpions were developed in collaboration with AstraZeneca (subsequently an AZ spin-out Dxs), and have been used in companion diagnostics. By determining the genotype of a cancer, this technology allows the clinical use of cancer drugs which were previously restricted on the basis of limited efficacy. For example, a Scorpion kit is used to group patients on the basis of their KRAS mutation status; and as a result of this the drug Vectibix® was approved for the KRAS wild-type population for which it is particularly effective. Similarly an EGFR kit is being used to establish the mutation status of non-small cell lung cancer tumours to determine likely response to the drugs Iressa® and Tarceva®. The Scorpion technology has been acquired by Quidgen who recently obtained FDA approval of the KRAS kit in the US for use with the colorectal cancer drug Erbitux®.

We are also working on the synthesis of analogues of DNA for therapeutic applications and we have recently started a project on the synthesis of next generation aptamers with the aim of specifically targeting cancer cells with drugs. In this project we aim to develop DNA and RNA aptamers with additional chemical functionality (such as hydrophobic – water-repelling - groups and hydrogen bonding residues) to increase target binding and selectivity beyond that which is achieved by the use of traditional aptamers.

**DNA Damage Signalling Group**

We aim to identify novel cell proliferation pathways to investigate drug resistance and predict response to chemotherapy and ionising radiation.

Our work focuses, in particular, on two processes relevant to cancer cell survival: (1) the role of ubiquitin–mediated proteolysis and (2) metabolism of desoxyribonucleotides (dNTPs). Further investigation into these processes will prove to be a powerful tool for the design and implementation of novel therapies.

Alteration of mechanisms monitoring cell cycle progression leads to cancer whereby cell proliferation is not integrated with checkpoint control signals. Instead cancer cells tend to proliferate in an uncontrolled fashion and become insensitive to external stimuli and checkpoint signals that ensure correct execution of the cell cycle. The ubiquitin proteasome system (UPS) lies at the heart of checkpoint mechanisms and dictates the fate of cellular proteins by tagging specific proteins with the small molecule ubiquitin. Single ubiquitin molecules are added via an enzymatic cascade, in which ubiquitin is activated by a covalent linkage to an activating enzyme (E1 ubiquitin) and transferred to a conjugating enzyme (E2 ubiquitin). The E3 ubiquitin ligases mediate the transfer to a lysine residue in the substrate from E2 ubiquitin to form polyubiquitin chains. Polyubiquitinated proteins are recognised for degradation by the proteasome (Figure 1).

Human cancers contain altered UPS components and E3 ubiquitin ligases, which highlights the relevance of these proteins in regulation of cell survival and proliferation. Furthermore the blockage of the UPS is currently exploited for the treatment of cancer through the use of bortezomib, a general inhibitor of the proteasome. Therefore, we are investigating the role of E3 ubiquitin ligases in cancer cell proliferation. Our studies will prove useful in developing effective therapies that specifically target the mechanism of action of E3 ubiquitin ligases and improve the efficacy of current approaches targeting the UPS.
DNA Damage and Repair

The long-term goal of our work is to study the coordination and regulation of Base Excision Repair.

Our research focuses on the study of the proteins and mechanisms involved in the coordination and regulation of Base Excision Repair (BER, Figure 1), to unravel their role in the repair of radiation-induced DNA damage and to examine the relationship to human diseases, such as cancer.

BER is a frontline DNA repair system that is responsible for maintaining genome integrity, thus preventing many human diseases, including premature ageing, cancer, and neurodegenerative diseases. It is estimated that through BER pathway a human cell repairs 10,000-20,000 DNA lesions every day. The majority of these lesions arise from the intrinsic chemical instability of DNA, resulting in DNA single-strand breaks, hydrolytic loss of DNA bases, base oxidations, non-enzymatic methylations and other chemical alterations. BER is also the principal DNA repair system in cancer cells that counteracts the killing effect of the major cancer treatments, i.e. chemotherapy and ionising radiation (approximately 80% of DNA damage induced by ionising radiation are DNA base lesions).

Changes in BER capacity most probably are responsible for many cases of cancer treatment efficiency, since many cancers have altered expression of BER proteins. Although BER enzymes have been studied in detail, the mechanisms involved in BER coordination and regulation are unclear.

The Biochemistry Laboratory has identified a novel molecular mechanism that regulates expression of BER proteins and coordinates DNA repair with the cell cycle progression (Figure 2). These studies are providing new insight into the biochemistry and regulation of DNA repair and how they impact cancer development and progression.

Exposure to ionising radiation (IR) can cause chromosome breaks, in which both DNA strands are broken. In addition to causing cell death (the desired outcome during radiation therapy) such lesions can also cause chromosomal rearrangements, a hallmark of cancer cells, which can lead to oncogene activation or tumour suppressor loss. We are examining the mechanisms and determinants of DNA double-strand break (DSB) repair in normal cells, and how misrepair can lead to chromosomal rearrangements, genome instability and cancer.

DNA is tightly wrapped up around proteins called histones to form chromatin. We have studied a chromatin mark, (histone H3 methylated on lysine 36), which is frequently lost in human cancers, most notably in more than 50% of high grade paediatric gliomas (childhood brain tumours). From our studies using fission yeast (Schizosaccharomyces pombe) we have found this mark to have an important role in DSB repair. Further, we identified a role for this chromatin mark in human cells in facilitating DSB repair within active genes across the genome and its loss leads to aberrant DSB repair associated with loss of genetic material. These findings are helping us understand how DNA damage can lead to chromosomal rearrangements, thus promoting tumourigenesis.

Further, we have exploited powerful genetic approaches (synthetic lethality) in yeast and human cells to identify drugs, which specifically kill cancer cells that are deficient in this chromatin mark. Using this novel combination of approaches we are now translating our findings into the clinic.

For more information about our research and details of publications, please go to www.oncology.ox.ac.uk
DNA Repair in Cancer Treatment Group

We are investigating DNA damage signalling and repair factors in bladder cancer to develop new radiotherapy-based treatments and to identify markers for personalised treatments.

Patients with muscle-invasive bladder cancer (MIBC) can be treated by surgical removal of their bladder or radiotherapy-based treatments. Radiotherapy has the advantage of bladder preservation. Adding chemotherapy to radiotherapy makes the tumour more sensitive to radiation and improves outcomes but adds to the side-effects of treatment. We have found that muscle-invasive tumours repair their DNA less efficiently than normal tissues and we are trying to exploit this difference by using radiosensitising drugs which target the remaining DNA repair pathways, thus damaging the tumour more than the surrounding normal tissues. Such drugs include gemcitabine, which is already in clinical use as a radiosensitiser and the histone deacetylase inhibitors. Further understanding of the mechanisms of action of these drugs will allow the development of more specific agents, which should result in reduced side effects.

We are also looking for markers in patients’ tumours which could help us predict which patients would benefit most from a particular treatment, and this could help patients make their choice between surgery and radiotherapy-based treatments. One such marker is the DNA damage signalling protein MRE11, which we have found predicted patient survival after radiotherapy but not surgery, in two groups of patients. We are testing this marker further in tissue from patients treated in two large randomised clinical trials. Muscle-invasive bladder tumours seem to have a shortened version of MRE11 and this could be important in terms of our clinical findings, so we are studying this in more detail. We have also found that a genetic variant of the MRE11 gene found in patients’ blood also predicted for radiotherapy outcomes and we are investigating the underlying mechanisms further. We are also exploring other predictive markers in tissue microarray samples from our patients, in an exciting Citizen Science project, where members of the public score our tumour samples, based on pattern recognition. Reverse the Odds is an award-winning mobile game developed by the Citizen Science team at CRUK in collaboration with Channel 4, Maverick TV and Crunch.

Cancer Cell Cycle Group

Research in our group focuses on the mechanisms that give rise to the abnormal proliferation characteristic of tumour cells.

An underpinning theme of our studies is that we believe, in order to design better therapies that effectively treat cancer, it is essential to decipher the molecular and biological details of pathways that control proliferation in normal cells and thereafter understand how they become aberrant in cancer.

A hallmark of tumour cells is evident in the control of the G1 to S phase transition, in normal cells this transition is tightly regulated whereas tumour cells progress liberally into S phase in an unrestrained fashion.

There are two key pathways of pivotal importance that govern progress through G1 into S phase, controlled by the retinoblastoma tumour suppressor protein pRb and the p53 tumour suppressor protein p53. pRb principally acts as a transcriptional regulator of the E2F family of cell cycle regulating transcription factors. In contrast, p53 is a stress-responsive transcription factor that activates genes involved with cell cycle arrest and apoptosis. Most tumour cells harbour mutations that alter pRb and p53 activity. Loss of pRb results in deregulated proliferation as a consequence of liberating E2F activity, whereas loss of p53 causes an insensitivity to checkpoint control.

The primary objective of our work is to explore the regulation of and control by pRb and p53 activity. Specifically, we have defined new levels of control in regulating pRb turnover suppressor activity, particularly novel post-translational signals. We have elucidated new members of the E2F family, and identified the key pathways through which they act. Functional characterisation of E2F in cell cycle control and apoptosis has identified a remarkable level of complexity that governs the switch to apoptosis. Our p53 research is principally focused on uncovering the diverse modifications that dictate the outcomes of the p53 response to stress.

We believe that biological knowledge on the mechanisms which drive cancer cell proliferation can be harnessed in designing new therapeutic modalities to treat cancer. Consequently, we work closely with the bio-technology and pharmaceutical sectors, together with clinical colleagues in translating our academic discoveries into an applied clinical setting. Drugs emanating from our earlier studies have been approved for haematological malignancy.

A major focus of our current work is to develop technologies that enable predictive biomarkers to be identified for cancer therapies. We have devised a genome-wide loss-of-function screen that identifies predictive biomarkers and deployed the platform to develop companion diagnostic tests for diverse cancer drugs.
**DNA Damage and Repair Group**

We aim to understand how repair of damaged DNA is controlled during chromosome duplication, and why potentially dangerous changes in cell behaviour can occur when this process goes wrong.

The DNA contained in our chromosomes holds our genetic blueprint (genome). Before dividing, cells must copy their DNA accurately to prevent changes being introduced into our genome. DNA damage can lead to errors being created during chromosome replication, including mutations that lead to cancer. Cells have evolved elaborate repair mechanisms to fix this damage and ensure that the genetic information is faithfully duplicated. Understanding these mechanisms has important implications for efforts to prevent cancer, while also helping to identify individuals who might be at increased risk of developing cancer.

A related aspect of our work focuses on improving cancer treatment. Many chemotherapy drugs and radiotherapy kill tumour cells by damaging their chromosomal DNA. For many cancer patients, such treatment improves their chances of survival, but sometimes these approaches fail. There is evidence that an increased capacity to repair the DNA damage induced by cancer therapies is an important factor in treatment failure.

One area of particular interest is the repair of DNA interstrand crossovers (ICLs), which are formed when the two strands of the DNA double-helix become covalently linked together. ICLs are an extremely toxic form of DNA damage that prevent fundamental processes including DNA replication. Defects in ICL repair result in cancer predisposition syndromes, such as Fanconi anemia, underlining the importance of ICL repair in human development and cancer avoidance. Conversely, many important cancer chemotherapeutics work through ICL formation. Together, these facts emphasise the importance of understanding ICL repair for improving cancer prevention and treatment strategies (Figure 1).

Related to these ICL repair studies, we have a major interest in a family of DNA repair factors that contain a metallo-β-lactamase fold. These factors, the human SNM1A (DCLRE1)-family nucleases, play a key role in processing β-lactamase fold DNA repair enzymes found in humans. The MBL fold is shown in blue and the distal β-lactamase fold DNA repair enzymes found in humans.

**DNA Repair and Replication Group**

We are investigating how cells resolve replicative stress arising from endogenous and exogenous sources and how failure to do so impacts on genome stability, cancer development and ageing.

Our research in genomic instability syndromes and development of cancer focuses on understanding the mechanisms disrupted in a childhood cancer predisposing syndrome named Fanconi Anemia (FA). Children afflicted with FA show developmental defects, progressive bone marrow failure and have up to 3000 fold increased cancer risk. This underscores the essential role of this pathway in suppressing tumour formation.

The genes mutated in this syndrome encode a network of ‘caretaker’ proteins, which not only ensure that DNA is accurately copied but also prevent replication failure and associated genomic instability. Consequently, a properly functioning FA pathway is important for normal development, haematopoiesis and suppression of solid tumours in everyone, and as such underscores the importance of research in this area.

We are particularly interested in how the repair of damaged DNA is executed in the context of the replication fork, and how fork stability is achieved under stressful conditions. To address these questions we are employing state-of-the art techniques that allow monitoring of DNA replication at the single molecule level in vivo (Figure 1). Using these approaches we aim to explain how the FA proteins function to promote DNA replication, and whether dysfunctional replication-mediated DNA repair is a common signal that drives FA disease progression to leukaemia.

A long-term goal of our research is to elucidate the FA-dependent mechanism required to suppress devastating haematological and malignant conditions and translate our basic laboratory findings into the development of novel therapies for cancer.

For more information about our research and details of publications, please go to [www.oncology.ox.ac.uk](http://www.oncology.ox.ac.uk)
DNA Damage Response Group

We are interested in the role of the ubiquitin-proteasome system in DNA repair, ageing, cancer and radiotherapy.

The research focus of this group is to understand the role of the ubiquitin-proteasome system (UPS) and its central component p97/VCP in genome stability. We aim to understand how we can use this knowledge to improve current cancer therapy, especially after ionising radiation. p97/VCP is a evolutionarily conserved segregase that with the help of specific cofactors binds and remodels (segregates) diverse and mostly ubiquitinated proteins (substrates) in a variety of cellular processes and compartments. In this way, p97/VCP and its cofactors play an essential role in the maintenance of protein balance (homeostasis) in the cell. We are especially interested in chromatin-related p97/VCP functions and consequently in chromatin-related protein homeostasis (Figure 1; p97/VCP-dependent chromatin-associated protein homeostasis) after DNA damage. Chromatin is the substance of a cell nucleus consisting of DNA, RNA and proteins, and the basic source of genetic information. Using biochemical and cell biological approaches we are investigating fundamental molecular aspects of protein homeostasis in DNA replication, DNA repair and DNA damage response. Mechanistic insights of basic cellular processes related to DNA metabolism and related protein homeostasis can improve our knowledge of ageing and ageing-related diseases as well as current diagnosis, prognosis and treatment of cancer.

We have identified the essential role of p97/VCP in chromatin and in DNA damage response, after ionising and ultraviolet radiation. We have discovered a new human syndrome characterised by premature ageing and early onset hepatocellular carcinoma (Figure 2; green arrow indicates tumour mass) that is caused by mutations in p97-cofactor SPRTN (Figure 3; genomic localisation of SPRTN gene). Our results strongly suggest that protein-induced chromatin stress (PICROS; pathological accumulation of proteins on chromatin) plays an essential role in cancer and ageing. The group is currently trying to understand how chromatin-associated protein homeostasis regulates PICROS and thus prevents accelerated ageing and cancer. We believe that understanding of PICROS might open new avenues in cancer diagnosis, prognosis and therapy, but also answer fundamental questions about ageing.

Genome Stability and Tumourigenesis Group

Our research is focused on how homologous recombination regulates telomeres and acts to prevent genomic instability.

The ability of cancers to tolerate DNA damage and grow, despite the accumulation of genetic errors, is a hallmark of human tumours. Our group is using genetic tools to determine how normal and tumour cells differ in their responses to DNA damage induced by ionising radiation (Figure 1).

Our focus is to define the cellular roles of homologous recombination genes, which protect us against cancer and are involved in repair of DNA lesions. Cells lacking these genes accumulate chromosome breaks (Figure 2). Mutations in BRCA2 gene in cancer cells promote breast tumours, whilst paradoxically the same mutations cause normal cells to stop dividing. We have been screening human genes to identify those which, when mutated, prevent cells from dying and cause cancer. If some of these genes are mutated in human tumours and if mouse models implicate them in tumour cell survival and proliferation, then this work could be a source of novel therapeutic targets that may prove more tractable, from a pharmaceutical point of view, than currently known tumour suppressors. Another major line of investigation in Dr Tarsounas’ laboratory is the action of homologous recombination proteins at telomeres. Telomeres are key structures at chromosome ends in all eukaryotes, consisting of repetitive DNA sequences and associated proteins. They are because they protect chromosome ends from degradation and fusion, both leading to chromosome mis-segregation, genome instability and onset of tumourigenesis. In addition, due to their repetitive and G-rich DNA sequence, telomeres pose an intrinsic barrier to genome replication. We are investigating how factors involved in homologous recombination facilitate successful completion of telomere replication, thus protecting genomic integrity. These studies are extended to analyse how telomere dysfunction (Figure 3), generated in genetically defined models for cancer development, can make cancer cells more vulnerable to killing by radiation therapies.

For more information about our research and details of publications, please go to www.oncology.ox.ac.uk

For more information about our research and details of publications, please go to www.oncology.ox.ac.uk
Like any other cells in the body, tumour cells are influenced by blood vessels and the normal cells and molecules that surround and feed the tumour cells – the tumour microenvironment.

Of all the cells found in solid tumours, tumour cells usually only account for 30-60%. The remainder are non-transformed (normal) cells such as fibroblasts, endothelial cells and immune cells. These normal cells are thought to have been commandeered by the tumour into playing a supporting role to help tumour growth, in many cases resembling a wound healing pathology with tumours referred to as 'wounds that do not heal'.

Endothelial cells (which allow the formation of new vasculature) are essential for the provision of oxygen and nutrients to the growing tumour, while fibroblasts (which are usually activated as 'myofibroblasts') are an essential source of extracellular matrix and growth factors that assist tumour growth. The immune cells that are present within solid tumours are usually inactivated by immune-suppressive mechanisms associated with other tumour cells and this provides an opportunity for immune 'reawakening' to create an anticancer immune response. This complex mixture of cells comprises what we call the tumour 'microenvironment', and the interplay of cells within the tumour microenvironment provides a range of new opportunities for therapeutic intervention.

Using the tumour microenvironment to identify novel therapeutic targets

Researchers in Oxford are investigating the tumour microenvironment in a number of ways. The ability of tumours to recruit a new blood supply provides an important point of therapeutic intervention that can severely restrict tumour growth and development. Innovative cancer killing viruses and oncolytic vaccines are being designed and developed to utilise the immune system to target tumour cells, leaving normal cells unharmed. This approach can be used in targeted cancer therapy in combination with biological agents.

Work is also underway to better understand signalling pathways within the cell and how alteration of these pathways can influence cancer onset and therapy. Gene mutations specific to lung cancer and changes in the microenvironment of pancreatic cancer are being exploited to identify novel therapies and optimise combination treatments including radiation therapy. The tumour microenvironment is also thought to be crucial to allowing spread of cancer around the body (the process of 'metastasis'), and the interaction of tumour cells with normal cells at sites of potential metastasis is a central research focus.

Earlier detection of metastases

Specialised imaging technologies are being used to identify and better understand microenvironmental processes that are involved in, for example, loss of local control, invasiveness and metastasis. Work is ongoing to advance and apply imaging methods for earlier detection of metastases. Furthermore, novel methods using radionuclides are being developed to enable imaging of proteins inside cancer cells, such as those involved in DNA damage repair signalling. It is hoped that advances in this area will enable both earlier detection and improved treatment of cancers.

Targeting hypoxia

A key focus of researchers in the CRUK/MRC Oxford Institute for Radiation Oncology is overcoming resistance to radiotherapy. Programmes are underway to better understand signalling pathways within the cell and how alteration of these pathways can influence cancer onset and therapy. Gene mutations specific to lung cancer and changes in the microenvironment of pancreatic cancer are being exploited to identify novel therapies and optimise combination treatments including radiation therapy. The tumour microenvironment is also thought to be crucial to allowing spread of cancer around the body (the process of 'metastasis'), and the interaction of tumour cells with normal cells at sites of potential metastasis is a central research focus.

Earlier detection of metastases

Specialised imaging technologies are being used to identify and better understand microenvironmental processes that are involved in, for example, loss of local control, invasiveness and metastasis. Work is ongoing to advance and apply imaging methods for earlier detection of metastases. Furthermore, novel methods using radionuclides are being developed to enable imaging of proteins inside cancer cells, such as those involved in DNA damage repair signalling. It is hoped that advances in this area will enable both earlier detection and improved treatment of cancers.

Targeting hypoxia

A key focus of researchers in the CRUK/MRC Oxford Institute for Radiation Oncology is overcoming resistance to radiotherapy. Programmes are underway to better understand signalling pathways within the cell and how alteration of these pathways can influence cancer onset and therapy. Gene mutations specific to lung cancer and changes in the microenvironment of pancreatic cancer are being exploited to identify novel therapies and optimise combination treatments including radiation therapy. The tumour microenvironment is also thought to be crucial to allowing spread of cancer around the body (the process of 'metastasis'), and the interaction of tumour cells with normal cells at sites of potential metastasis is a central research focus.
Radiopharmaceuticals and Molecular Imaging Group

We aim to develop new radioisotope-labelled compounds for the imaging of tumour biology using nuclear medicine imaging techniques.

Molecular imaging using the nuclear medicine imaging techniques of single photon emission computed tomography (SPECT) and positron emission tomography (PET) allows the visualisation and quantification of biological processes in tumour tissue in living organisms. The main advantage of these non-invasive techniques is that they can be performed repeatedly in the same subject, and that the same imaging methods are used in the clinic, which makes them easier to translate from the laboratory to patients in the clinic. Because of their exceptional selectivity and sensitivity, we are mostly interested in the use of antibodies, proteins and peptides, labelled with radionuclides, to target very specific aspects of tumour biology.

Usually, molecular imaging targets are extracellular epitopes: cytokines, growth factors, or extracellular receptors. However, there is a mismatch between molecular imaging methods, which mostly target proteins or receptors on the outside of cancer cells, and cancer biology, where mostly intracellular events are studied. Therefore, one aim of the group is to develop novel methods to enable imaging of intracellular proteins, such as those involved in DNA damage repair signalling.

Furthermore, increased awareness and the rolling out of screening programmes have had a significant impact on cancer survival, especially breast cancer. The earlier a cancer is detected, the better the chances for survival are. Another aim of the group is therefore to develop methods that would allow early detection of tumour tissue.

We are evaluating the novel imaging agent developed in the group in models of breast and pancreatic cancer.

Tumour Hypoxia Group

We are investigating how tumours survive in conditions which include hypoxia. Our goal is to target the hypoxic parts of tumours to improve cancer therapy.

Although tumours are able to create their own blood supply this process is not perfect and so tumours have regions which do not receive enough oxygen. Hypoxia is the term used to describe any situation where there is insufficient oxygen. Most solid tumours have regions of hypoxia (Figure 1), which is significant because many studies have shown that the more hypoxic a tumour is, the worse the patient does. Importantly, this is independent of the therapy type the patient receives. Hypoxic tumours are resistant to both chemotherapy and radiotherapy as well as being more likely to spread and are therefore the most aggressive and hardest to treat. To improve the effectiveness of cancer therapy it is vital that we target the hypoxic part of tumours. Our group has three approaches to this problem:

1. We are investigating the biological response to hypoxia and in particular a pathway known as the DNA damage response. This pathway is active in hypoxic conditions despite a lack of detectable hypoxia-induced DNA damage. There are many drugs to target this pathway and it is possible that they will prove particularly useful in killing hypoxic cells when combined with standard therapies such as radiation.

2. We are developing novel drugs which only work in the absence of oxygen and so can be used to target the hypoxic areas of tumours. This approach allows us to use potentially toxic drugs as the normal cells in the body are unaffected.

3. Finally, it is vital that novel inhibitors/drugs are tested in conditions which mimic those found in tumours. Therefore, we test drugs in conditions which more closely resemble those found in tumours, including low oxygen, to determine if they are likely to be effective.

For more information about our research and details of publications, please go to www.oncology.ox.ac.uk
Growth Factor Group

The focus of the group is on tumour angiogenesis and the role of notch signalling, and hypoxia biology and its regulation.

The aim of our research is to develop ways to improve the treatment of breast cancer and other tumour types, by blocking the blood supply to tumours. Our special interest is in breast cancer and mechanisms of resistance to therapy, regulated by hypoxic metabolism and tumour angiogenesis, when tumours cannot grow without a new blood supply developing from pre-existing blood vessels.

Our research focuses on tumour angiogenesis and the role of notch signalling, and hypoxia biology and its regulation. New angiogenesis pathways involving notch signalling and G-coupled receptors have been discovered and therapeutic antibodies have been developed against them. We want to translate these basic discoveries into clinical relevance.

Hypoxia regulates many oncogenic pathways, as well as tumour angiogenesis, and it produces major metabolic changes. The latter may be responsible for resistance to endocrine therapy, chemotherapy and radiotherapy through different pathways. Our preclinical programme investigates several of these, and particularly those involved in lipid and glycogen metabolism. These provide new therapeutic avenues that will be assessed in Phase 1 and Phase 2 studies.

A major interest is in new angiogenic therapies, and developing ways to determine who will most benefit from these targeted therapies. Our work assesses the short-term effects on imaging with novel scanning agents, and biopsies for gene expression, then relates tumour response to longer term outcomes. In addition, metabolic profiling will be undertaken in patients to correlate the responses to new therapies with imaging changes and for individualisation of therapy.

Preclinical work has indicated combination therapy is significantly better and that the expression of hypoxia may induce a synthetic lethality approach, targeting the hypoxic pathways induced by antiangiogenic therapy. Many of these are also involved in the induction of hypoxia biology. The metformin study started because metabolic changes induced by Avastin® could be antagonised by metformin and combination therapy may therefore be a useful new modality. However, patients will respond differently to metformin based on the cancer cell biology and we want to try to identify those who show the clearest benefits and elucidate the pathways responsible.

Molecular Resistance to Treatments Group

Our research links basic science with clinical applications and focuses on understanding the mechanisms behind tumour resistance to radiation.

The main goal of our research is sensitising cells to radiation by blocking mechanisms that control cell survival. Specifically we are interested in oncogenically activated signal transduction pathways that exert a radioprotective effect on tumour cells. The effectiveness of radiotherapy treatment could be significantly improved if tumour cells could be rendered more sensitive to ionising radiation without altering the sensitivity of normal tissues.

In the past, our research has shown that the EGFR-Ras-PI3K-AKT pathway appears to be the major radioprotective pathway active in most solid tumours, and therefore this pathway presents targets that could be manipulated in a clinical setting to modify the radiation response. We have shown that a specialised DNA repair enzyme, DNA polymerase theta (POLQ), is overexpressed by tumour cells and that depletion of this enzyme makes cells more sensitive to radiation. Importantly, normal healthy cells do not appear to express POLQ and are therefore not affected by its inhibition. We also found that patients with high levels of POLQ expression have a worse prognosis. This would make POLQ an ideal therapeutic target for improving the effectiveness of radiotherapy without increasing normal tissue toxicity.

We are also interested in improving radiotherapy by reducing tumour hypoxia (low levels of oxygen in the tissue). One of the main reasons for the resistance of tumours to radiotherapy is the presence of large hypoxic regions that are significantly more resistant to radiation. One way of alleviating tumour hypoxia is to reduce the oxygen consumption of the fast growing cells at the tumour periphery so that more oxygen becomes available to the hypoxic regions. A way of alleviating tumour hypoxia is to reduce the oxygen consumption of the fast growing cells at the tumour periphery so that more oxygen becomes available to the hypoxic regions. A high throughput screen conducted by our laboratory identified drugs that reduce oxygen consumption in tumour cells that could be used clinically to reduce tumour hypoxia.

Gillies McKenna
Gillies McKenna, Professor of Radiation Oncology and Biology, has been Director of the CRUK/MRC Oxford Institute for Radiation Oncology since 2005 and Head of the Department of Oncology at the University of Oxford since 2010. Prior to that, he was Chairman and Henry K. Pancoast Associate Professor of Radiation Oncology at the University of Pennsylvania School of Medicine, rising to Professor in 1995. He has received several awards and honours including the Weiss Medal from the Association for Radiation Research, the Frank Ellis Medal from the Royal College of Radiologists, the Roentgen Medal from the Deutsches Roentgen Museum and the Gold Medal from the Royal College of Radiologists.
Mechanisms of Metastasis Group

We are interested in the mechanisms underlying the development of metastasis, the spread of cancer from one part of the body to another.

Our research focuses on the interaction of cancer cells with the host vasculature and the circulating blood cells. The interactions between tumour cells and the host vasculature are important in the initiation of metastases (secondary cancer) as well as allowing metastatic colony growth later in metastatic progression. Our work has indicated the importance of coagulation and platelets in recruiting myeloid cells to allow the earliest formation of metastatic colonies. Later in metastasis, recruitment of myeloid cells is also essential for colony growth and the formation of blood vessels in the colonies. We are asking how these myeloid cells enable metastatic progression. This work is beginning to identify targets both for detection and for treatment of metastatic lesions.

Tumour vascularity is essential for the response of cancers to radiation therapy. During therapy, hypoxia (low oxygen) is highly detrimental to effective radiation therapy. Hypoxia is of course determined by tumour vascularity and oxygen consumption. We have begun to develop strategies to reduce hypoxia during radiation by identifying agents that lead to better blood vessel formation, also called vascular normalisation, and strategies to reduce tumour oxygen consumption. These strategies would be expected to generate tumours that are less hypoxic and more responsive to radiation therapy. Clinical trials are underway based on this work.

The final outcome of radiation therapy is also affected by tumour regrowth at the end of therapy. We have shown that inhibition of vascular regrowth leads to enhanced efficacy of radiation therapy. We are currently exploring the mechanisms that tumours treated with radiation use to stimulate vascular growth and the means to interfere with this growth.

Cell Signalling Group

We aim to understand the cell and molecular biology behind frequent tumour mutations and how they influence cancer onset and therapy.

For cancers to develop, cells must acquire mutations and epigenetic alterations that prevent the normal control of proliferation and survival. While there are multiple signalling pathways that could be targeted for mutation, there are key genes that are recurrently altered in tumours. Our research focuses on the most frequent and clinically relevant events to understand how alteration of signalling pathways contributes to disease onset and affects treatment outcomes.

RAS is a family of proteins expressed in all cells. Our work focuses on how oncogenic RAS activation combines with tumour suppressor events such as loss of p53 function to allow tumour growth and invasion. By understanding these common events we aim to better define patients’ cohorts and provide a scientific rationale for personalised medicine approaches. In particular, we have been exploring this within a multidisciplinary team tackling pancreatic cancer.

Figure 1: Tumour cell (green) metastatic to the lung endotheium (red) surrounded by platelets (blue).

Figure 2: Loss of RASSF1 expression correlates with loss of the YAP partner and differentiation factor, RUNX2 in colorectal adenocarcinomas. Normalised expression levels with red = upregulation and blue = downregulation.
Lung Cancer Research Group

Our group aims to identify novel therapies that target subgroups of lung cancer patients harbouring specific genetic changes.

Our research focuses on lung cancer where our primary aim is to identify new drug targets and to determine how best to integrate novel therapies with current standards of care in lung cancer, and to optimise combination treatments including radiation therapy. During its development, lung cancer acquires activating mutations that are critical for continued tumour growth. For example, recurrent mutations have been described in several key oncogenes (including EGFR, Kras, ALK, BRAF, PIK3CA and ERBB2). Since these activating mutations are not found in normal tissues, we are currently screening for combinations of novel compounds that can selectively kill these cells while leaving normal cells unaffected. Importantly, lung cancer can also acquire loss of function mutations in tumour suppressor genes. As a consequence, tumour cells become highly dependent on compensatory signalling pathways, which might then be targeted in order to kill the tumour cells. In contrast, non-tumour cells without the tumour suppressor gene mutation, are less dependent on these compensatory pathways and therefore are relatively unaffected by pathway inhibition. We are currently screening for targets and compounds that can lead to selective killing of tumour cells with tumour suppressor gene mutations that are common in lung cancer (e.g. TP53, LKB1, ATM).

To study drug effects we also need to be aware of potential effects on normal tissues. In the case of radiotheraphy for lung cancer, debilitating scarring known as fibrosis can occur throughout the lung several months after treatment. So in addition to seeking therapies to improve the effectiveness of radiation, we are also examining the impact on lung function using advanced imaging and histological techniques.

Translating findings from the laboratory to the clinic is an ongoing challenge in cancer research. So, in addition to standard cell lines, we are also working with samples derived directly from lung cancer patients so that we may be able to better predict responses in the clinic.

Anticancer Viruses and Cancer Vaccines Group

Our research aims to design and develop innovative cancer-killing viruses and oncolytic vaccines.

Our research develops anticancer ‘oncolytic’ viruses that are able to infect and kill cancer cells, while leaving normal cells unharmed. This approach exploits the natural life cycle of the virus, which lyses infected cells and releases progeny virus particles, allowing the infection to spread from cell to cell through the tumour. In this way the virus amplifies itself locally, reaching higher concentrations within the tumour than in the bloodstream during delivery – a very unusual feat for an anticancer drug.

Virus replication maximises therapeutic anticancer activity and simultaneously minimises unwanted systemic side effects. This represents the ultimate ‘magic bullet’, combining selectivity of action with a big amplification of activity at the tumour site.

The life cycle of some viruses, such as adenoviruses, is intimately dependent on the activities of the cells they infect, and this provides a range of opportunities to engineer oncolytic viruses that are only active when they encounter the specific cellular environment of a tumour cell. For example, adenoviruses can be designed that are dependent on deregulated cell cycle, dysfunctional apoptosis pathways, enhanced glycolytic metabolism and many others. In addition, this ‘oncolytic’ type of cell killing is very inflammatory, providing the possibility to create an anticancer immune response. These agents are often known as ‘oncoviclanticides’.

To allow therapeutic use in treating advanced (metastatic) cancer, we give special attention to developing viruses that can be administered intravenously to patients. To achieve this it is important that the virus can survive the challenging environment of the human blood circulation, and also that virus particles are not cleared too quickly from the circulation, before they have a chance to access tumour deposits.

Finally, our viruses can be ‘armed’ to encode additional therapeutic agents, to be expressed only within the tumour and secreted from infected tumour cells into the microenvironment. In this way we can achieve targeted expression of therapeutic biologics such as cytokines, antibodies and enzymes, to augment the activity of the virus itself. This provides a simple and versatile approach to targeted cancer therapy, allowing the power of biological agents to be applied locally within tumours and avoiding unwanted toxicities.
Experimental Neuroimaging Group

Our goals are to identify the role of the inflammatory and metabolic microenvironment in brain metastasis, and to develop imaging biomarkers for tumour detection and monitoring.

Metastasis (secondary cancer) to the brain is a significant clinical problem and prognosis is extremely poor. The incidence of brain metastasis is increasing as patients survive longer, and even radiosurgery/radiotherapy has limited impact on prognosis.

We have identified three critical hurdles to effective treatment of brain metastases: (1) late stage of diagnosis; (2) poor access to the brain (bioavailability) of therapies that are successful in peripheral tumours; and (3) impact of microenvironmental factors on the effectiveness of treatment. By improving our understanding of the microenvironment of brain metastases, we believe that we will not only identify new therapeutic targets, but also drive the development of diagnostic imaging tools for use in patients.

Earlier detection of brain metastases is likely to yield substantial gains both for current therapies and the development of new metastasis-inhibiting agents. To this end, we have demonstrated that it is possible to detect brain metastases at a much earlier stage than current clinical methods allow, through the use of new molecularly-targeted imaging agents (Fig. 1).

In collaboration with others in the University, we developed and patented biodegradable microparticles of iron oxide (MPIO) as a platform for translating this technology to man. Together, this work has formed the basis of two successful applications to the MRC Developmental Pathways Funding Scheme to progress this agent to a Phase I/IIa clinical trial.

Figure 1(A): Confocal microscopy images showing co-localisation of the cellular adhesion molecule VCAM-1 (red) on vessels associated with a micrometastasis (green) in mouse brain. Cell nuclei stained blue. (B): MRI detection of VCAM-1 expression on brain blood vessels using VCAM-1-targeted MPIO in a mouse model of brain metastasis; 3D reconstruction showing spatial distribution of VCAM-MPIO binding (in red) indicating sites of metastases throughout the brain.

In collaboration with others in the University, we developed and patented biodegradable microparticles of iron oxide (MPIO) as a platform for translating this technology to man. Together, this work has formed the basis of two successful applications to the MRC Developmental Pathways Funding Scheme to progress this agent to a Phase I/IIa clinical trial.

Figure 2: SPECT image showing accumulation of radiolabelled Trastuzumab at the site of a micrometastatic colony in mouse brain following selective permeabilisation of the metastasis-associated vasculature.
A key aim of the Department of Oncology is the optimal translation of fundamental research into patient benefit. Precision cancer medicine brings together the concepts of biological selection of therapy with targeting of treatment to deliver the best possible outcomes for a patient with cancer. Clinical research builds on the themes of DNA damage and repair and the tumour microenvironment and encompasses genomics, biomarkers, imaging and clinical trials. Computational biology, which sits at the interface of all these, generates essential knowledge in the pathway to providing cutting-edge clinical treatment for cancer patients.

Biomarkers and personalised medicine

Patients are individuals – made unique by their signature genes and proteins. In the same way, cancers have specific characteristics. Even within one type of cancer, not all patients will respond to the same treatment in the same way and response to therapy is influenced both by the individual patient and the cancer’s characteristics. In order to select the right treatment for the right patient at the right time, we need to identify biological factors or biomarkers that can predict how an individual patient will respond to a particular drug or radiotherapy regime. The treatment can then be tailored to achieve the best outcome for each patient.

Researchers in Oxford are using existing, and developing new, biomarkers to select patients for therapy in both early and late phase clinical trials. Specific biomarkers are used to group patients into subtypes of a cancer, which can be used to guide participation in appropriate clinical trials. This may be with a new agent that promises benefit for the patient’s particular subtype of cancer.

Advancing imaging technologies in patient treatment

Imaging techniques play a central role in cancer research and treatment. Imaging is often the first means of detecting a tumour and is used to provide accurate information about the location and extent of the tumour (anatomical imaging) and the cancer’s behaviour (functional imaging). Imaging is used, therefore, to guide treatment decisions, to drive the anatomical precision of treatment for surgery and radiotherapy, and to monitor response to treatment – detecting tumour shrinkage or growth (progression).

Researchers are also developing advances in techniques of radiotherapy planning coupled with advanced tumour imaging to deliver the radiation more precisely to predetermined volumes within the tumour. This reduces side effects and improves the outcome for the patient. The Department is fortunate to be home to the CRUK & EPSRC Cancer Imaging Centre in Oxford. Since 2008, this highly successful initiative has nurtured multidisciplinary collaborations with the common goal of improving imaging and image analysis and has provided a focus for translational work.

Clinical trials

The Department’s clinical research programmes initiate and develop high quality clinical trials to test hypotheses emerging from the basic science research groups. The aim is to improve the effectiveness of radiotherapy and chemotherapy in the treatment of cancer.

Clinical activities are underpinned by the Department’s Oncology Clinical Trials Office (OCTO) and the Early Phase Clinical Trials Unit (EPCCTU), which together, provide the necessary infrastructure and expertise to set up and run studies in Oxford and throughout Europe.
Cancer Therapeutics and mRNA Dysregulation

**We investigate post-transcriptional mechanisms that drive cancer behaviour and research novel cancer therapeutics for patients with advanced malignancies.**

**mRNA Dysregulation in Cancer**

Gene expression describes the conversion of genetic message to protein. This depends on messenger RNA (mRNA) which copies the gene sequence, shuttles into the cytoplasm, binds ribosomes and generates protein. Numerous RNA binding proteins (RBPs) attach to these mRNA transcripts and regulate their splicing, stability, subcellular localisation and rate of translation.

In cancer cells, expression of RBPs is disrupted, driving the malignant state by preserving the stability of proto-oncogenic mRNAs while destabilising those with tumour suppressor functions. One such RBP is La-related protein 1 (LARP1). We have shown that LARP1 is capable of selectively binding transcripts involved in cancer processes and is present at high levels in some epithelial cancers. The net effect of LARP1 upregulation is to drive cancer progression.

The purpose of our research is to discover more about cancer RBPs and develop therapeutics against them that can be used as anticancer treatments.

**Cancer Therapeutics**

A crucial part of cancer drug discovery is finding the best cancer treatments for the future. In leading the Early Phase Clinical Trials Unit, Sarah’s team investigates new treatments for patients with cancer. Potential treatments are carefully chosen on their scientific rationale, their likelihood of being effective and, most importantly, their safety profile. The Oxford Early Phase Clinical Trials Unit has a long established track record of drug discovery and delivering novel therapies safely and effectively. Sarah has a strong science and medical background which enables her to design clinical trials, investigate treatments developed by academia or industry and deliver them to cancer patients.

**Cancer and Immunogenetics Laboratory**

**We focus on the fundamental genetics and biology of colorectal cancer and the characterisation and distribution of genetic diversity in human populations.**

The fundamental genetics and biology of colorectal cancer (CRC) and their potential applications

We use a panel of over 100 colorectal cancer (CRC) cell lines to study the basic biology of colorectal cancer as well as the effects that new treatments have on the cancer cells. The cell lines have been extensively characterised for genetic mutations, expression profiles and growth characteristics. The use of this number of cell lines allows the identification of subsets of cancers that behave similarly with respect to their biology, drug responses and growth characteristics. This, in turn, allows us to identify the molecularly-defined profiles that correlate with, and can ultimately be used to predict for, those responses. Cancer stem cells can be isolated from within individual cell lines and we are also trying to identify the genes that control stemness and cellular differentiation in CRC.

Recently, we have developed a protocol that allows efficient establishment of medium to long-term primary cultures from fresh CRC tumour material. These are now being compared with the cell lines, both with respect to their biological properties and their drug responses.

The characterisation and population distribution of genetic diversity in human populations, especially of the British Isles

We have collected DNA samples from people in rural areas of the UK whose grandparents all come from within a small geographic radius. This is to reduce the effects of interbreeding between diverse populations, which has the effect of removing ancient regional differences. This serves as a very effective set of healthy controls for genetic studies into the causes of common diseases such as diabetes, psoriasis and schizophrenia. We have analysed Single Nucleotide Polymorphism data from our samples and shown a strong connection between geography and genetic variation. The genetics of normal differences, particularly facial features, are also being investigated; to this end, we are assembling a database of 3D photographs from volunteers whose genotype data we also have.
Oncological Image Analysis

We develop image analysis methods for quantitative analysis of medical images, specifically for a range of applications in cancer.

Image analysis based on MRI, CT, PET, SPECT, ultrasound, and various forms of microscopy, is firmly established as a basis for detection and diagnosis of disease and for illustrating aspects of the fundamental science basis of cancer. In practice, much of image analysis is qualitative in that it relies upon the judgement of experts to interpret the images.

We aim to develop precise measurements from images, enabling us to: monitor the progression of disease; measure the response to therapy; and to estimate physical aspects of tumours, such as their size and density. Some of many examples of our work include: measuring from a mammogram the amount and distribution of dense tissue in the breasts of post-menopausal women (currently regarded as one of the main risk factors for breast cancer); identifying complete responders to neoadjuvant chemotherapy in colorectal cancer (potentially avoiding major surgery); and classifying liver textures, such as those characteristic of a range of liver diseases.

Figure 1 illustrates some of our quantitative analysis of breast density estimated from a single mammogram. Note that the volumes of fibroglandular tissue is expressed in cm³ while the x-ray dose estimated as a result of this particular mammogram is 2.8 mGy. Our work forms the basis of the products of VolparaSolutions, a company we founded in 2008 based on science we did in Oxford starting in 1993.

Figure 1: (Left) A mammogram; at point a, we estimate 3.6cm fat, 2.4cm of dense tissue; at point b, 5.8cm of fat; characteristic of a range of liver diseases.

These applications rely upon, and motivate the development of, advances in image analysis techniques: image segmentation, feature extraction, deformable image registration, atlas development, and tumour modelling. Figure 2 shows the vasculature computed automatically for one slice of an MRI volume of the liver. This is used subsequently to detect and stage liver disease.

Figure 2: (Left) A mammogram; at point a we estimate 3.6cm fat, 2.4cm of dense tissue; at point b, 5.8cm of fat; characteristic of a range of liver diseases.

Figure 3: (Right) Quantitative measurement of the amount of dense tissue in the breast.

Computational Biology and Integrative Genomics

We search for integrated genomic blueprints that enable us to predict how cancer will evolve and respond to treatment.

High throughput technology has supported a scientific revolution both in molecular biology and clinical research. In molecular biology, and more specifically in both cancer and radiobiology, it is now possible to acquire data at the whole genome level, and to characterise a genomic blueprint for different cancer types. This has allowed us to ask questions on how the cancer genome is regulated. Most importantly, we are beginning to understand how and where the blueprint of the genome is functional and what the biological and clinical implications of this function are.

In translational and clinical research it is becoming increasingly possible to acquire both genomic and disease imaging data, and this combination can provide further understanding of the molecular and clinical cancer phenotype. This revolution has enabled the accumulation of cancer genomic big data and related knowledge at a speed never experienced before in science. The knowledge generated with this big data is being increasingly organised in both specialist and general knowledge databases which can be interrogated by computational tools.

We are investigating integrative approaches to combine results from functional assays, systems level approaches and clinical knowledge with genomics (DNA) and transcriptomic (RNA) data. To achieve this we apply a wide range of sophisticated computational and statistical techniques to analyse large clinical cohorts. Our research sits at the interface between genomics, imaging and biomarkers and is applied to molecular and radiation oncology.

Our more recent work focuses on next generation sequencing techniques and high content screening, and the development of tools to aid the translation of this big data generated knowledge into beneficial use in the clinic for treatment of patients.

The graph shows the interplay between genes regulated by hypoxia in a cancer cell. Genes are shown as circles, while their relationship with co-partners genes which help fuel progression of cancer is shown by grey edges. The network demonstrates complex interplay which emerges when the cancer cell undergoes hypoxia following poor blood supply, and patients with such deregulation are shown to have a poorer outcome. A computational algorithm previously developed by us (Buffa et al) was used, which aims at unravelling such interplays by starting with known key player genes (in red) exhibiting similar patterns of expression, and further filtering to those genes having the highest number of associates/co-partners. This way, a highly active network is identified which is shown to contain primary culprits of driving aggressive cancers.
Precision Radiotherapy Physics Group

Our work focuses on high precision radiotherapy and molecular imaging of tumour function and treatment response, with a particular focus on lung cancer.

The last 20 years have seen profound advances in the technological foundations of radiation oncology, allowing the quality of radiotherapy dose distributions to be raised to levels limited only by the fundamental physics of radiation transport.

Radiotherapy of advanced non-small cell lung cancer (NSCLC) has achieved poor results historically, and while modern treatments have produced better outcomes there is much room for improvement. Our group has designed dose-escalated accelerated treatments of NSCLC, which utilise advances in X-ray beam technology to deliver increased radiation doses in short (24-6 week) schedules. These treatments have recently been clinically trialled with promising results, a median survival of 39 months for advanced stage disease being achieved by a moderately escalated concurrent chemoradiation treatment.

We are working on further improvements, focusing on radiotherapy dose painting, proton beams, and novel hybrid magnetic resonance imaging-linear accelerator systems (MR linacs). Dose painting seeks to focus high levels of radiation on treatment-resistant tumour subvolumes—an approach that will improve outcomes if position emission tomography (PET) imaging can be used to accurately identify regions of enhanced tumour glucose utilisation, proliferation (growth) or hypoxia (low oxygen levels). Factors all associated with treatment resistance.

Beams of high energy protons offer great opportunities for further improving radiotherapy. However, development of on-the-fly image guidance is required to obtain the best results for NSCLC, to ensure that critical normal structures are excluded from rapidly moving target volumes, which can potentially be very highly irradiated using protons. Initially we are seeking to develop this form of image guidance for MR linacs and to deliver mixed proton-X-ray treatments, combining the improved physics of proton beams with the enhanced imaging available on X-ray MR linacs.

Pancreatic Cancer Research Groups

We are investigating the mechanisms of tumour progression and resistance to radiotherapy and chemotherapy to improve the clinical outcome of patients with pancreatic cancer.

Pancreatic cancer is a leading cause of cancer death and has the lowest 5-year overall survival rate (6%) amongst major cancer sites worldwide. Approximately 8,000 cases of pancreatic cancer are diagnosed each year in the UK. Despite rapid advances in oncology, the outcome in pancreatic cancer has changed very little over the last 40 years. The basic and translational aims of the Fokas Group are to: 1) identify the mechanisms that mediate response of pancreatic cancer to radiotherapy and chemotherapy; 2) test and validate rational combinations of novel targeted agents with radiotherapy and chemotherapies to develop efficacious therapeutic strategies; and 3) explore ways to sensitize pancreatic tumours that are resistant to conventional therapeutic approaches. We are particularly interested in the desmoplasmic tumour microenvironment and the inflammatory and immune response, as the immunosuppressive desmoplasmic microenvironment can facilitate tumour growth and resistance to conventional therapies.

Somnath’s key area of interest is developing early phase clinical trials involving radiotherapy and drug/radiotherapy combinations in pancreatic cancer and upper gastrointestinal cancers. He has experience as Chief Investigator or Co-Investigator in recruiting patients for early phase trials in pancreatic and gastro-oesophageal cancers. As a Chief Investigator of the CALGB trial and co-leads for radiotherapy for the ESPAC-5 trial, Somnath has already influenced national practice by introducing chemoradiotherapy as an option for locally advanced pancreatic cancer in the UK. He has brought together a national group of radiation researchers with interest in this disease site.

Somnath also has collaborations with clinical scientists and science groups involved in: preclinical development of novel radiosensitisers in upper GI/pancreas, signal pathways in radiosensitivity/radioresistance, hypoxia, development of peripheral blood biomarkers/circulating tumour DNA for radiation response and novel imaging for early detection of radiation response resistance.

Figure 1: A-B, Examination of hypoxia using bioluminescence imaging and immunostaining with the EF5 antibody. (In red) and a nuclear stain (in blue). C-D, Functional analysis of tumour vasculature by 3D-Doppler and multiphoton microscopy of C3H10T1/2 fibroblasts cultured on matrigel. (In red) and a nuclear stain (in blue). E, Flow-cytometry analysis of immune markers in pancreatic cancer. F, Serography in the KPC mouse model of pancreatic cancer. G, CT image, merged CT-MRI images and the simulation of radiation dose distribution around the KPC tumour stained red (blue) are shown.

Figure 2: A, A parametric map showing the variation across a tumour of the tracer-to-counter ratio which nominally describes phosphorylation of the radiotracer 32P/32P-P by the enzyme thymidine kinase 1, whose expression is closely linked to proliferation. The map was calculated from dynamic PET images collected during the hour following tracer injection.
Novel Clinical Imaging Research Group

Our group focuses on using imaging techniques in small-scale trials with the particular ambitions of improving the mechanisms of data analysis and correlating the imaging data provided with histology and treatment outcomes.

There are now an unprecedented number of imaging techniques being developed that are potentially available for clinical practice, for instance, dynamic contrast enhanced MRI, perfusion CT, novel PET tracers, and hyperpolarised xenon. These techniques have yet to be shown to impact on clinical practice and often require modification of either scanning technique or methods for data analysis. There is also a significant amount of data available from current imaging techniques already in use that may potentially be used as a prognostic biomarker, predict treatment response, and modify treatment.

Figure 2: (A) Fluorodeoxyglucose PET-CT images of a patient with bilateral scapula bone metastases from renal cancer. Image A shows the anti-angiogenic effect of treatment with decreased integrin activity at the sites of pre-treatment avidity. A is pre-antiangiogenic therapy demonstrating active angiogenesis at the edge of the metastases. Image B confirms the anti-angiogenic effect of treatment with decreased integrin activity at the sites of pre-treatment avidity.

We have focused on a small number of different areas: angiogenesis imaging, using dynamic contrast enhanced MRI and perfusion CT, dynamic FDG PET imaging, and the novel 153PET-PET imaging agent fluciclatide (Figure 1).

We have also developed novel data analysis techniques for use in hyperpolarised xenon MRI (Figure 2). Trials in normal healthy volunteers, patients with COPD and lung cancer are currently underway, and have enabled us to develop methods of lobar analysis of ventilation and emphysema correlated with CT and pulmonary function. The aim is to develop an imaging tool that would, for instance, predict the change in lung function following lobar resection or following radiotherapy.

Figure 2: 3-D hyperpolarised xenon ventilation MRI image

Technical Radiotherapy/Advanced Radiation Oncology

Personalising gastrointestinal cancers radiotherapy: the ultimate aim of the research of my group is to maximise clinical benefit in terms of better tumour control and reduction in toxicity after radiotherapy to enhance life expectancy of the patient.

Despite several advances in techniques of radiotherapy planning (intensity modulated radiotherapy), tumour imaging (PET, MRI), radiation delivery (rotational arc therapy) the techniques and doses used for radiotherapy treatments of gastrointestinal malignancies cancers have remained unchanged. Chemoradiation remains the main treatment for inoperable patients and the outcomes in tumours such as oesophagus or pancreas have not improved over the last decades. The causes of local failure are due to several aspects: inadequate radiation dose, low oxygen levels (hypoxia), failure to target areas that have an unfavourable microenvironment. The advances in technology, imaging and understanding of biological processes offer an opportunity to novel approaches.

The aim of my research has three main themes with the ultimate aim of maximising clinical benefit in terms of better tumour control and reduction in toxicity.

1. Strategies of modulating radiotherapy (SMART): Radiotherapy dose escalation techniques using Simultaneous Integrated Boost permits intensification of radiotherapy dose to predetermined volumes within the tumour, derived from biological imaging such as PET or functional MRI. Tumour control probability/normal tissue control probability models can be then used to refine the dose escalation within the tumour further and spare normal tissue exposure. The dose escalation is being tested in the Phase 3 clinical trial SCOPE2 for oesophageal cancer in collaboration with Dr. Crosby in Cardiff.

2. Margin targeted radiotherapy concept. The use of stereotactic ablative radiotherapy to areas at risk of not being completely cleared with surgery, with the aim of achieving complete tumour resection. This is tested in a Phase 1 trial in the preoperative setting for tumours that are difficult to clear due to proximity to critical organs.

3. Refining normal tissue toxicity modelling in thoracic malignancies: The objective of this work is to characterise and corroborate lung, heart and oesophagus radiotherapy toxicity parameters and develop individualised radiotherapy delivery techniques to minimise dose to susceptible heart, oesophagus and lung substructures. This would allow selecting the best radiotherapy dose delivery technique in patients receiving combined chemoradiation and surgery.

Figure 3: Standard dose radiotherapy treatment plan for a multi-organ cancer patient. The dose scale is from 0 Gy (blue) to 50 Gy (orange) to 65 Gy (red).

Figure 4a: Increased radiotherapy dose may be delivered using SMART techniques to the central high risk volume with no increase in dose to the surrounding tissues. The dose scale is from 0 Gy (blue) to 50 Gy (orange) to 65 Gy (red).
Tumour Radiosensitivity Research Group

Our research focuses on finding new ways of making tumours more sensitive to radiotherapy treatment.

Radiotherapy is a core component of treatment for many cancers, but radioresistance, due to naturally occurring genetic or epigenetic changes in tumour cells and extrinsic radioresistance, due to tumour low oxygen levels (hypoxia), can significantly reduce the efficacy of radiotherapy. Our laboratory research focuses on exploring ways of overcoming radioresistance of tumour cells with a view to finding new ways of making tumours more sensitive to radiotherapy treatment.

We have undertaken large scale siRNA screens to better understand intrinsic radioresistance and identify novel ways of making tumours more sensitive to radiotherapy. We have found several new genes that are involved in increasing tumour cell death after drug treatments that we feel will reduce the hypoxic fraction in the tumour. This work also works as an Honorary Consultant Clinical Oncologist specialising in the management of lung cancer in Oxford University Hospitals NHS Trust. He previously undertook medical training at the Edinburgh Cancer Centre before moving to Oxford as a Cancer Research UK Clinical Research Fellow in 2007.

Figure 2: 18F-Misonidazole PET-CT scan showing a large left upper lobe tumour with lymph node metastases. Hypoxic areas of the tumour are represented by red regions on the scan.

We are also interested in finding innovative ways of reversing tumour hypoxia which reduces radioresitivity of the tumour. In addition to conducting laboratory work looking for novel drugs that reduce hypoxia, we are also undertaking clinical trials exploring new drug treatments that we feel will reduce the hypoxic fraction in the tumour. This work typically uses functional imaging, such as perfusion CT scans and 18F-Misonidazole PET-CT scans, to detect changes in tumour blood flow and regions of tumour hypoxia, respectively (Figure 1). By performing these scans before and after drug treatment we can assess from the 3D images over time whether hypoxia has been reduced in the tumour thereby making the tumour more likely to respond beneficially to radiotherapy.

We have found several new genes that are involved in increasing tumour cell death after drug treatments that we feel will reduce the hypoxic fraction in the tumour. This work

Adjuvant Colorectal Cancer Group

We are working towards delivering the right treatment to the right patient at the right time.

Adjuvant therapy is given after surgery in order to decrease the risk of recurrence and improve overall long-term survival. Adjuvant therapy can comprise cytotoxic and non-cytotoxic drugs as well as radiotherapy, the latter being of great interest for other Groups within the Department of Oncology.

Great progress has been made in the adjuvant colorectal cancer field over the last 25 years as we can now save a further 35-20 lives per 100 patients treated compared with surgery alone. However treatment is often delivered at great cost, both in terms of financial cost in a resource restricted environment, and toxic cost in terms of morbidity and mortality of patients undergoing such treatment. Therefore it is imperative that we not only improve the paraply (array) of drugs we can offer, but also refine our ability to predict which patients will gain most benefit from which drugs. Additionally, we need to predict which patients will suffer greatest toxicity, allowing us to dose reduce drugs a priori, or in some cases to avoid certain drugs altogether.

Throughout all of our large scale trials we collect blood and DNA for genetic profiling and also tumour tissue. This allows us to carry out highly powerful translational research and lends us the scope to define the biomarkers as outlined above. In addition to furnishing our own research, these huge biobanks with extremely clean and reliable clinical data can be mined by other researchers.

Recent and planned trials include:

1) QUASAR2: Assessing the addition of bevacizumab (Avastin®) in the adjuvant treatment of colorectal cancer.
2) SCOT: Assessing whether 3 months of adjuvant therapy can give equivalent efficacy compared to the standard 6 months of chemotherapy in the adjuvant treatment of colorectal cancer, thereby reducing toxic and financial cost.
3) COLOSELECT: A planned multinational trial looking at the efficacy of aspirin and vitamin D in biomarker-selected populations of colorectal cancer.
Insulin-like Growth Factor Group

We are studying the role of insulin-like growth factor (IGF) signalling in tumour biology, aiming to exploit this information in the management of patients with cancer.

The main aim of our research is to understand the contribution of insulin-like growth factor (IGF) signalling to cancer biology. Production of IGF-1 from the liver is regulated by growth hormone, and people with congenital deficiencies of growth hormone or IGF-1 are strongly protected from developing cancer. IGF-1 binds to type 1 IGF receptors that are expressed on the surface of cancer cells, activating intracellular signalling pathways that promote cell growth, invasion and resistance to killing by cancer treatments.

We have shown that IGF receptors are upregulated in prostate and renal cancers, and detectable in advanced primary tumours and metastatic disease. We also demonstrated that IGF receptors undergo ligand-dependent import into the nucleus of human tumour cells, and nuclear IGF receptor is associated with adverse prognosis in renal cancer. These findings suggest a link with aggressive tumour behaviour, and we are currently investigating the role of IGF receptor in the nucleus.

Our other major interest is to develop approaches to exploit IGF receptor and related signalling molecules as targets for cancer treatment. Our research aims to identify factors that influence sensitivity to drugs that block IGF receptor, and test IGF receptor inhibition (as a route to chemoradiosensitisation). We recently showed that IGF receptor inhibition delays the repair of DNA double-strand breaks, apparently independent of its well-known ability to regulate apoptosis induction. Understanding the basis of this effect may enable effective exploitation of this approach in the clinic.

We are also contributing to the establishment of a Preclinical Validation Core in the Department of Oncology. The aim is to provide preclinical support and optimisation for clinical trial proposals, such as the evaluation of targeted agents in new indications and/or novel combinations.

Clinical Research Programmes

We aim to deliver a step change in the effectiveness of radiotherapy through the evaluation of novel scientific approaches derived from the Institute’s scientists in hypothesis-driven clinical trials.

The CRUK/MRC Oxford Institute for Radiation Oncology’s vision is to improve the chances of cure for patients with cancer through scientifically valid and novel ways of improving the effectiveness of radiotherapy. We are concentrating on some of the hardest to treat cancers, particularly those arising in the lung, gastrointestinal tract and bladder where radiotherapy makes an important contribution to treatment.

Improving effectiveness: We are pursuing three main ways to improve outcome from radiotherapy:

• The major advances in radiotherapy in the past 30 years have been through improved technical accuracy leading to reduced side effects. We are testing higher dose treatment using intensity modulated and stereotactic radiotherapy treatment and proton beam therapy. We have completed a clinical trial [Footnote] of targeted radiotherapy to the liver using yttrium-90 labelled microspheres.

• Low levels of oxygen (hypoxia) in the cancer make it resistant to radiotherapy and more likely to spread. We have shown in lung and pancreas cancer that use of novel targeted drugs which inhibit the PI3K kinase-AKT pathway can improve oxygen delivery and reduce hypoxia.

• Radiotherapy causes DNA damage in the cancer and normal tissues. Cancer cells are often less effective at repairing damage. As novel drugs that target DNA damage repair show a marked improved response to radiotherapy in laboratory tests, we are planning to test these in patients with oesophageal cancer.

Precision Cancer Medicine: We are working on selecting approaches which can predict a person’s response to treatment based on functional imaging and biomarkers to help provide the right treatment for the right person at the right time.

• Imaging hypoxia using PET scans has enabled us to prove that hypoxia is altered through both drug and radiotherapy treatment. The degree of hypoxia and how it changes early in a treatment will help us select patients for hypoxia-modifying therapy.

• Biomarkers, which can be measured from tumour tissue or the circulation, may guide selection of the appropriate patients for specific therapies.

Colorectal cancer: Tim leads two national research studies in colorectal cancer. The MRC FOCUS4 trial started to recruit patients in 2014. It uses a novel trial design to evaluate treatments suitable for patients with molecularly-defined subgroups of colorectal cancer. The MRC-funded stratified medicine consortium will be investigating biomarkers to identify those patients likely to benefit from either chemotherapy (oxaliplatin), radiotherapy, minimal surgery or novel drugs in the treatment of colorectal cancer.
Early Phase Clinical Trials & Melanoma Therapy

Our Group’s research concentrates on development of new cancer drugs and on the treatment of melanoma.

Early phase clinical trials

Our aim is to bring the excellent science in Oxford to cancer patients. Our strategy is to develop new treatments or combinations of treatments through the concepts of ‘synthetic lethality’ and oncogenic vulnerability.

To deliver this we have established the infrastructure to perform detailed analyses of tumours before, during and after intervention to select patients, to test our a priori hypotheses, and to better understand the biological effects of treatment.

Melanoma trials

Recently we have seen incredible advances in the treatment of advanced melanoma. The challenges now are to understand why not all patients benefit from the new drugs at our disposal.

 Genetic characteristics or signatures are being explored to identify patients who are likely to benefit from particular treatments, and to make informed treatment decisions on the best combinations of drugs to use in the clinic. For example, we have defined new combinations of radiotherapy with vandetanib and of paclitaxel with trametinib, and are active in the development of new drugs such as IMCgp100, MLN0430, T-Vec and IMM47. We are looking into biological markers to identify patients most likely to benefit from bevacizumab therapy in the national AVAST-M study, starting with those whose melanoma has a mutation in the BRAF gene.

In close collaboration with radiation oncologists within the Department of Oncology and the Churchill Hospital, we are planning, conducting and analysing a range of clinical trials acquiring a range of functional imaging ([18F-FDFOG PET, DCE MRI and perfusion CT]) for a number of diseases including rectal, anal, pancreatic and oesophageal cancer. Data from these trials is being used to learn which imaging modality (or combination) gives the most useful information for either guiding individual patient treatments or for monitoring biological response during therapy, allowing treatments to be adapted to optimise response based on the biological profile of individual patients.

Radiotherapy Physics Research Group

We apply functional and molecular imaging techniques to developing radiotherapy personalised to each patient’s individual tumour biology.

Medical imaging has for a long time played an absolutely central role in radiotherapy. Radiation treatments are carefully planned using patient-specific information from x-ray computed tomography (CT). An accurate 3D computer model of each patient’s anatomy is made using the CT data, with the tumour and surrounding normal organs carefully identified. Radiation treatments are then designed and simulated by computer before being delivered in the clinic. Advances in magnetic resonance imaging (MRI) and positron emission tomography (PET) now enable us to map not just patient anatomy but also physiological function, giving important information about the biochemistry of tumours as well as their physical characteristics (size and location).

For example, we know that regions of tumours that have low oxygen levels (hypoxic) are often resistant to both radiotherapy and chemotherapy. By imaging hypoxic tumour regions we can monitor response to therapy and, for patients who do not appear to be responding to treatment, either escalate radiation dose or add a hypoxia-modifying drug (or both). Dynamic contrast-enhanced (DCE) and diffusion-weighted MRI can be used to map blood flow and perfusion properties and diffusion in tissue, telling us about oxygen supply. PET can be used to map glucose metabolism using positron emitting radiolabelled tracers such as fluorine-18 labelled fluoro-2-deoxyglucose ([18F-FDG]) and hypoxia usingfluoromisonidazole ([18F-FMISO]).

In collaboration with radiation oncologists within the Department of Oncology and the Churchill Hospital, we are planning, conducting and analysing a range of clinical trials acquiring a range of functional imaging ([18F-FDFOG PET, DCE MRI and perfusion CT]) for a number of diseases including rectal, anal, pancreatic and oesophageal cancer. Data from these trials is being used to learn which imaging modality (or combination) gives the most useful information for either guiding individual patient treatments or for monitoring biological response during therapy, allowing treatments to be adapted to optimise response based on the biological profile of individual patients.
Oxford Molecular Diagnostics Centre

The aim of my research group is to identify molecular-based disease classifiers using clinical omics to direct treatment of patients and precision medicine.

As the Director of the Oxford NHS/BRC Molecular Diagnostics Centre (MDC), Anna Schuh leads on a translational research programme for the development, validation, standardisation and evaluation of clinical utility of next generation technologies and clinical omics. Her laboratory has developed the first fully certified next generation sequencing multigene panels for use in NHS diagnostics of cancer and a number of haematological malignancies.

The MDC has been designated an NHS England Genomic Medicine Centre and partners with Genomics England in the implementation of whole genome sequencing technology to provide NHS diagnostics. A particular focus of the laboratory is to define molecular-based disease classifiers for cancers and haematological malignancies that underpin precision medicine approaches including risk stratification and rational treatment design. Using samples from National Cancer Research Network (NCRN) clinical trials, her group is also interested in the evaluation of the clinical utility of whole genome sequencing and was first to publish longitudinal studies of whole genome sequencing (WGS) from chronic lymphocytic leukaemia (CLL) patients undergoing treatment. A current focus of the laboratory is to further characterise hyper-mutated non-coding region in the CLL genome and to examine total RNA expression in CLL.

In her role as the clinical lead for CLL and other lymphoproliferative disorders for the Oxford NHS/BRC Molecular Diagnostics Centre (MDC), Anna is a Principal Investigator on a number of early and late phase clinical trials in CLL and the Director of the Oxford NHS/BRC Molecular Diagnostics Centre (MDC). She receives grants from NIHR, Wellcome Trust and the Technology Strategy Board. She is an active member of the NCRN CLL subgroup she leads in the Genomics England 1000 subgroup she leads in the Board. She is an active member of the NCRN CLL subgroup she leads in the Genomics England 1000

Translational Biomarker Development Group

We are developing and validating novel diagnostic tests and new imaging techniques to select patients likely to benefit from certain cancer therapies and radiotherapy.

Our research group’s focus is on the translation of biochemical knowledge of DNA damage repair to the selection of patients for certain cancer treatments. The group has developed several tissue biomarkers for the personalisation of chemotherapy and radiotherapy which are being tested in clinical trials. Laboratory studies are ongoing in parallel with clinical studies of radiosensitisers to be used in the treatment of colorectal cancer, liver metastases and oesophageal cancer. New functional and dynamic imaging techniques are being tested in clinical trials led by Professor Sharma. These include:

- FOXFIRE, a phase 3 trial comparing chemotherapy alone (5-fluorouracil, oxaliplatin and folic acid) with chemotherapy plus radioembolisation for colorectal cancer that has spread to the liver. Radioembolisation (also called selective internal radiotherapy or SIRT) delivers radiation directly to the cancer cells in the liver. This novel approach minimises radiation dose to normal liver tissue.
- PERFORM, a pilot study exploring the feasibility, safety and effectiveness of a novel computed tomography (CT) scanning technique called perfusion CT in patients having SIRT treatment. This approach aims to evaluate if the tumour perfusion pattern at baseline or shortly after the start of therapy can predict response to radioembolisation or chemotherapy.
- SONATINA, a phase 1-2 clinical trial which aims to investigate the safety and the activity of the radiosensitising drug, nelarabine, administered before and during radiotherapy in patients with rectal cancer. As well as establishing the safety of this novel treatment combination for patients with rectal cancer, an additional aim of the study is testing the feasibility of a new biomarker measured in tumour tissue, Tumour Cell Density (TCD).

For more information about our research and details of publications, please go to www.oncology.ox.ac.uk
Experimental Radiation Therapeutics Group

We apply functional and molecular imaging techniques to developing radiotherapy personalised to each patient’s individual tumour biology.

Our primary goal is to develop radiopharmaceuticals to image and treat cancer. We have designed and synthesised investigational imaging probes that are directed against a range of cancer targets including DNA damage signalling proteins such as nucleolin, the ErbB family of receptors, angiogenesis (development of new blood vessels) and telomerase (involved in cell ageing and cancer) among others. We have a particular interest in developing antibody-based imaging probes through our participation in the CRUK & EPSRC Cancer Imaging Centre in Oxford. Another focus is the development of techniques for targeting intracellular and, in some cases, intranuclear molecular targets for imaging through the use of cell-penetrating peptides, among other strategies. Some tumour-seeking probes that we develop may be used for the treatment of cancer as well as imaging. We have worked with therapeutic radionuclides which emit radiation such as Auger electrons, β electron- or α-particles. To be effective as therapeutic agents, radionuclides must accumulate in a cancer in sufficient quantity to deliver a tumouricidal dose of radiation. Through our work within the EPSRC Oxford Centre for Drug Delivery Devices (OxCDT), we are investigating radiolabelled nanoparticles, in combination with physical stimuli such as ultrasound, to enhance intratumoral drug release and delivery. A major interest of the group is in the development of clinically applicable dosimetry systems for molecularly targeted theranostic agents. We are investigating novel methods for the detection of radionuclides at the subcellular, cellular and whole tissue levels. An understanding of the dose distribution at the nanometre to micrometre scale is particularly important for those therapeutic radionuclides that emit α-particles or low energy particles, such as Auger electrons.

We use a combination of novel autoradiography approaches and Monte Carlo modeling to understand how the distribution of radionuclide in a single cell or multicellular situations determines their radiobiological effect. Our work in this area is also currently directed to understanding how to combine radionuclide therapy with external beam irradiation.

For more information about our research and details of publications, please go to www.oncology.ox.ac.uk

Radiation Therapy Medical Physics Group

Our research group specialises in bringing fundamental physical concepts to enhance everyday clinical practice.

The main concept we take is a physics approach. The model is used to provide predictions outside of the current measurement set and thereby test the model, which has the minimum number of parameters needed to describe the experimental data. While this is the standard practice of scientific methodology, we keep the ultimate clinical applicability of the concept in mind.

Fundamental concepts: One area of research is a first principle approach to quantifying DNA damage induction by irradiation with different types of ionising radiation (photons, protons, α-particles), in such a way that it can be used in clinically relevant environments. In addition, confounding factors like the level of oxygen (as low oxygen levels confirm radio-resistance) and repair altering chemicals. The models can take these confounding factors into account. Another area of research is the use of the notion of alpha-stable distributions which are used to parametrise treatments and provide mathematical models for the robustness of external beam treatments.

Applied Work: The fundamental work is developed in a number of applied projects using dose calculations (Monte Carlo simulation and biological effects through DNA damage estimates), imaging using new equipment to allow visualisation of tumour and tumour changes during treatment, and proton therapy. Our group is strongly involved in the building of the proton therapy arm of the Precision Cancer Medicine Institute (PCMI), mainly concentrating on the possibility of low impact treatments of breast and haematological cancers (Hodgkin’s Lymphoma + Non-Hodgkin’s Lymphoma).

Clinical Implementation: Implementing concepts directly in the clinic where we introduce imaging during treatment to allow physicians to use models based on the change in texture to adapt the treatment using biological quantities (treatment response) rather than only physical ones (patient position, geometry changes). Also the robustness of models allows the planning process to be adapted to provide patient-individualised treatment margins.

For more information about our research and details of publications, please go to www.oncology.ox.ac.uk
Our work focuses on the application of novel imaging modalities and on the development of radiation delivery methods. Both of these are dependent on a range of interrelated technologies.

Preclinical image-guided ionising radiation delivery systems are being developed, mimicking increasingly accurate patient radiotherapy. Numerous associated technical problems relate to dose delivery to small tissue volumes that ‘move’ due to breathing. We have developed sensors of this motion, coupled to very fast radiation beam gating. The accuracy of the radiation delivery critically depends on the quality of target imaging; conventional methods of cone beam CT are being complemented by optical fluorescence, ultrasound and other imaging techniques.

Fluorescence optical image guidance has also been developed for use during human surgery (Figure 1). Here we exploit the near infrared region of the optical spectrum (650-950 nm) to allow real-time imaging at tissue depths of <20 mm. This has been applied to lymph node imaging. An exciting new development is molecular optical imaging of prostate tumours to ensure that the surgeon is able to perform correct excision of extra-prostatic tumour tissue.

Time-resolved fluorescence microscopy techniques have been developed and enhanced over many years. Once excited by a light pulse, a fluorophore carries on emitting fluorescence light for a few nanoseconds. The kinetics of this process inform on resonance energy transfer between suitably chosen fluorophores tagged to proteins of interest (Förster Resonance Energy Transfer, FRET). This is strongly dependent on the inter-fluorophore distance and the method can be used as a molecular ruler, capable of measuring distances of 1-10 nm, way below any competing methods. We have developed medium throughput, high content automated microscopy platforms to allow protein interaction screening of patient biopsies (Figure 2). The aim here is to determine which drugs are likely to be effective at treating the cancer.

We have also developed a unique system, based around an in-house 6 MeV electron linear accelerator coupled to a robot and fluorescence microscopy, to study radiation-induced cell DNA repair kinetics using high resolution time-lapse imaging (Figure 3). We can resolve double strand breaks formed within seconds and are able to follow the temporal evolution of the repair of individual breaks.
The Department’s world-leading scientific cores and specialist facilities provide essential support, expertise and knowledge to our research programmes. They afford the added value of in-house partnership and expert advice on developing experiments, designing equipment, maintaining cutting-edge technology and providing clinical support.

The strength of our facilities comes from a combination of outstanding staff and state-of-the-art equipment, which together enable support for basic science through to studies focused on patient benefit and clinical trials.

Our expertise is broad-ranging and multidisciplinary. It spans diverse activities, including analysis of biological samples with complex techniques such as HPLC and flow cytometry, establishment of validated assays for use in clinical studies, and modelling of cancer systems biology using computational genomics. We provide imaging at the cellular and whole body level using advanced microscopy techniques and multiple imaging platforms, including MRI, and we also have unique skills in developing radiation resources and techniques for both imaging and radiotherapy.

In addition to these physical activities, which are supported by a fully equipped mechanical engineering workshop, we have expertise in clinical trial design, optimisation and management as well as a busy, experienced early phase clinical trials unit that provides patient care and plays an important role in the development of innovative cancer treatments.

We have invested heavily in these facilities to underpin the expanding department and provide comprehensive support for our key areas of focus in cancer research: DNA damage and repair, tumour microenvironment, and clinical and translational research. Through a combination of funding sources, a number of new facilities have been created across the Department since 2014.

The Microscopy Core has been successful in consolidating state-of-the-art equipment and providing dedicated, skilled microscopists to optimise studies and capitalise on the available technology.

The challenges associated with the half-life of some radiolabelled agents have signalled the need for an in-house radiopharmacy unit. Once open, the PET Radiochemistry and Radiopharmacy Core will enable on-site production of radiolabelled pharmaceuticals and tracers for use in biological evaluation and clinical trials.

The Preclinical Validation Core has been established to optimise the design of both preclinical studies and clinical trials, using a combination of in vitro and in vivo methods. Additionally, support for our translational activities has been provided through the formation of the Clinical Radiotherapy and Clinical Imaging Cores. Their focus is on improving clinical delivery through trials and the development of novel radiotherapy techniques, such as proton beam therapy, and advanced imaging techniques, including MRI, CT and PET.
Bioanalysis Core

We provide support in flow cytometry and in high performance liquid chromatography-mass spectrometry (HPLC-MS).

The Bioanalysis Core works with research groups across the Department and also supports a number of clinical studies. Flow cytometry can determine how actively the cell is growing, how immature processes are proceeding, whether any abnormalities are occurring, and if necessary isolate a population of interest for further study. The flow cytometry laboratory consists of three flow cytometers and a cell sorter. The HPLC laboratory operates as a controlled access facility in order to allow the maintenance of GCLP standards required for clinical studies. It is used for determination of cellular metabolites, and to measure the distribution of drugs in blood and tissues (pharmacokinetics) in clinical trials. New analytical methods are developed as required, and we also offer expertise in drug formulation and stability studies, and to confirm compound identity. There are three HPLC systems with coupled mass spectrometry, and a fourth HPLC offers alternative detection techniques.

Bioinformatics Core

We provide expertise in computational biology ranging from applied statistics to computational and functional genomics.

The Bioinformatics Core supports investigators in the Department of Oncology in all aspects of bioinformatics through development of collaborative and independent research projects. We maintain state-of-the-art computational approaches to cancer systems biology and clinical trials to ensure coordination of experimental and analytics approaches through different phases of a research project. Increasingly, much of our research is related to individualised medicine such as an *omics assessment of cancer patients. We focus on development of strategies for genomics data analytics, statistical algorithms for primary data analysis and interpretation, as well as on biological and clinical data integration to provide a richer and more comprehensive understanding of cancer aetiology and progression.

Clinical Radiotherapy Core

We support the implementation of clinical trials involving novel applications of radiotherapy or novel radiotherapy techniques including proton beam.

The Clinical Radiotherapy Core sits at the interface of the CRUK/MRC Oxford Institute for Radiation Oncology and the NHS radiotherapy department under the leadership of Dr Frank Van den Heuvel, the Head of the NHS Radiotherapy Physics department.

The team works closely with the Radiation Oncology Group and associated staff funded by both University and NHS to support the development and implementation of the Institute’s clinical trials and those of the national trial portfolio (NIHR Clinical Research Network). The core is increasingly focusing on proton beam therapy, undertaking comparative planning studies of photons and protons to identify subsets of patients where proton therapy has clear cut advantages as a basis for clinical trials in these areas.

Clinical Imaging Core

We support the development and implementation of advanced imaging techniques in clinical trials.

A new clinical imaging core is currently being established and will sit at the interface of the CRUK/MRC Oxford Institute for Radiation Oncology and the NHS Radiology department. The team will be led by Dr Mike Partridge (physics), Dr Ricky Sharma (oncology) and Professor Fergus Gleeson (radiology).

The team will support the development, implementation and analysis of advanced imaging techniques in magnetic resonance imaging (MRI) (spectroscopy, hyperpolarised xenon, dceMRI, shMOLLI), computerised tomography (CT) (perfusion), and positron emission tomography (PET) imaging (dynamic FDG, FMISO) in clinic trials supported by multiple funders. Close collaboration with the Institute of Biomedical Engineering (Professor Julia Schnabel), The Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) and commercial sources enables state-of-the-art techniques and analysis to be introduced into our studies.
GCP Laboratories

Our goal is to accelerate the development of new cancer treatments by establishing validated assays for cancer biomarkers that can be used to evaluate clinical utility.

The aim of the Oxford Experimental Cancer Medicine Centre (ECMC) GCP Laboratories is to describe the distribution and prognostic impact of markers in patient sample collections and evaluate their predictive potential in clinical trials. In order to deliver GCP compliance over the whole translational research process we collaborate with research groups to develop protocols that will produce samples of optimum quality for analysis in validated assays.

Our main areas of biomarker development and validation include tumour marker analysis by automated immunohistochemical staining, and analysis of circulating biomarkers using ELISA. Other studies include western blot analysis of cell signalling proteins and fluorometric detection of drug analytes.

We work with small phase 1/2 clinical trials and larger phase 3 studies and collaborate with groups to either carry out the whole study from development through to analysis of the trial samples, or to provide training on the use of the facilities for translational work.

Early Phase Clinical Trials Unit

We aim to support the translation of research findings into clinical practice.

The Early Phase Clinical Trials Unit (EPCTU) supports academic and commercial research predominantly in patients with oncological and haematological cancers. The unit provides expertise in regulatory submission with most trials now being set up in under 12 weeks. The clinical space comprising of 10 beds is highly rated by patients as delivering quality care in a comfortable environment.

There is a sample handling facility co-located on the ward which enables a high sample throughput with record keeping, to demonstrate custodianship of the samples, allowing for quality analysis.

A team of research nurses and clinical fellows work across the broad portfolio of studies, providing expertise in patient management and protocol compliance. By taking a systematic approach to data capture, data entry is highly compliant and the team is trailing real-time data entry.

Imaging Core

We provide routine technical support services and operate a programme of advanced method development in order to optimise the use of the imaging facility.

The Imaging Core is equipped with three Magnetic Resonance Imaging (MRI) systems, Positron Emission Tomography-CT, Single-Photon Emission Computed Tomography-CT, optical and ultrasound imaging, conventional and focused radiotherapy instruments, and a fully automated 100 Tb data storage and distribution system. We are staffed with specific expertise in vivo biology, MR physics and engineering, and image analysis physics.

To maximise the utility of imaging in preclinical research, we develop new and better scanning techniques that reduce the impact of body motion and provide improved quantitative measurements of disease progression and the response to treatment. We are currently deploying these advances to enable multimodal image-guided radiotherapy of preclinical models of cancer, and to improve the clinical relevance and translational capabilities of the Department’s research.

Mechanical Workshop

We provide support ranging from design to manufacture and assembly.

The Mechanical Workshop assists numerous scientific groups, supporting experimental, preclinical and clinical studies. It offers a ‘total package’ from design consultation, computer modelling, computer-generated drawings, material sourcing, manufacture and assembly. Its facilities include state-of-the-art machinery and innovative 3-D computer-aided design (CAD) packages and computer-aided manufacturing (CAM) software tools.

Work with ionising radiation, specialised preclinical imaging and indeed specialised clinical activities all require the development of highly specific assemblies and components. Work carried out within the Mechanical Workshop is diverse and can range from production of a peculiar optical adaptor or sample jig to manufacture of a complete radiotherapy delivery machine.

In addition to item manufacture, the workshop offers design using CAD software tools, allowing the end user to have a complete perspective of their item prior to manufacture.

For more information about our research and details of publications, please go to www.oncology.ox.ac.uk
Microscopy Core

We aim to provide research groups with imaging technologies to investigate cellular processes both in vitro and in vivo.

The Core is a facility established in 2014 which provides high quality research into innovative and effective cancer therapies. We have a variety of systems including wide-field microscopes for time-lapse imaging of processes such as cell division, highly sensitive optical sectioning laser scanning confocal microscopes and a multi-photon microscope for deep tissue in vivo tumour imaging. We also provide commercial image processing software for data analysis. We are developing the facility to include new technologies such as super-resolution microscopy and have strong links within the Oxford imaging community to share our resources and expertise.

Sarah Pearson
Thi Management Director of OCTO

Graham Brown
Microscopy Core Leader

Graham Brown established the Microscopy Core in 2004. He has a background in cell biology and has worked with Bio-Rad, Leica and Zeiss in their advanced microscopy groups.

Oncology Clinical Trials Office (OCTO)

We provide clinical trial management support to investigators from concept to completion.

OCTO was established in 2002 to run trials concerned with the practical application of high quality research into innovative and effective cancer therapies. We work with investigators to deliver trials in medical oncology, radiotherapy and imaging from first-in-human drug trials to large phase 3 clinical studies across a range of tumour types. We have particular expertise in delivering early phase multi-centre trials for biologically distinct populations. By working with over 250 hospitals and collaborating with research communities, industry and patients to support the work of the CRUK Oxford Centre, CRUK/MRC Oxford Institute for Radiation Oncology and the Oxford Biomedical Research Centre, OCTO is the oncology division of the UKCRC registered Oxford Clinical Trials Research Unit (OCTRU) and a member of the NCRI Cancer CTUs Working Group.

Sarah Pearson
Thi Management Director of OCTO

Graham Brown joined OCTO in 2004 and took on the role of Trial Manager Director for the unit in 2008. Before this she worked for Cancer Research UK on cancer genetics and epidemiology.

PET Radiochemistry and Radiopharmacy Core

We support radiochemistry-dependent research programmes and provide GMP-grade PET radiopharmaceuticals for clinical trials.

Currently under construction, the Positron Emission Tomography (PET) Radiochemistry and Radiopharmacy Core will be located at the Churchill Hospital alongside the PET-CT centre to enable translational research of radiotracers between the Department of Oncology and the Oxford University Hospitals NHS Trust.

The research and development labs will offer specialist radiosynthesis equipment, allowing the development of radiotracers and their production for in vitro and preclinical research. We will transfer innovative radioactive protocols developed by our collaborators in chemistry to widen the portfolio of radiotracers available for biological evaluation.

Radiotracers for human administration will be produced in the Good Manufacturing Practice (GMP) labs since they must fulfil strict criteria for patient use. The facility and its team will provide proven PET imaging agents for trials and develop, validate and manufacture new tracer candidates.

Rebekka Hueting
PET Radiochemistry and Radiopharmacy Core Leader

Rebekka Hueting joined the Department of Oncology in 2014 to establish the PET Radiochemistry and Radiopharmacy Core. She obtained her DPhil on the synthesis of radiotracers for oncology and held a postdoctoral research fellowship at King’s College London and Oxford.

Preclinical Validation Core

Our aim is to meet the need for rapid translation of key aspects of basic science to the clinic.

We work with clinicians and scientists to generate in vitro and in vivo data necessary to validate concepts emerging from basic research, and to optimise the design of in-house clinical trials. We assist in planning appropriate project proposals for further preclinical and clinical studies.

In vitro work: We have access to large panels of cell lines and are committed to a comprehensive range of techniques including primary and 3D cell culture, which may more accurately predict clinical outcome.

In vivo work: This builds upon in vitro results, focusing on new approaches for treating cancers using novel drug therapies as well as combinations with previously established drugs or radiotherapy. The Core is embedded within the laboratories of Valentine Macaulay and Anderson Ryan.

Frances Willenbrock
Lead Scientist

Frances Willenbrock joined the Department of Oncology in 2014 and previously held a Wellcome Trust Career Re-entry Fellowship at the CRUK London Research Institute.
Radiation Biophysics Core

We facilitate radiation research within the department and investigate the health implications of human exposure.

The Radiation Biophysics Core develops and supports a unique range of radiation resources and techniques along with providing associated expertise. These facilities range from those used for basic cell irradiations (including techniques capable of manipulating radiation fields on the sub-cellular micron scale), through to supporting and developing a SARRP image-guided preclinical x-ray irradiator and also includes developing techniques for dosimetry on clinical machines.

One of the main research interests includes investigating how and why ionising radiation initiates a diverse range of biological responses. We are also interested in how this correlates to differences in the temporal and spatial pattern of energy deposition events on the scale of DNA, cells and tissues associated with different radiation qualities of ionising radiation. Mechanisms are thus formulated which are interpreted in the context of risk associated with exposure or which can potentially be exploited in radiotherapy.

Mark Hill
Radiation Biophysics Core Leader

Mark Hill is the Radiation Biophysics Core Leader, the chief examiner for the MSc in Radiation Biology and has been involved with a number of national and international committees on radiation.

Localization of DNA repair protein (RAD51) to damage in a cell nucleus following alpha-particle traversal, with insert showing a schematic of the alpha-particle track interacting with DNA, producing clustered damage.
Our four year DPhil in Oncology programme has an annual intake of approximately 24 students. We have studentships funded by Cancer Research UK, the MRC, Oxford’s prestigious Clarendon Fund, and a number of joint scholarships with Oxford colleges. We also attract a large number of externally-funded students with Commonwealth or Government funding, or with Rhodes, National Institutes of Health (NIH) or Marshall Scholarships. We hope to increase these studentships as the Department continues to expand.

We offer our promising graduates a broad range of multidisciplinary and translational cancer research projects. As a result, our graduates come from a wide range of scientific backgrounds including biology, medicine, engineering, mathematics, chemistry and physics. By coming to the Department of Oncology they work alongside and learn from leaders in their field, and we provide them with a world-class academic environment and the best support services, including a comprehensive portfolio of personal and professional skills development.

Training the next generation of scientists and clinicians to become leaders in cancer research is central to the Department of Oncology’s mission.

The Department of Oncology, which includes the CRUK/MRC Oxford Institute for Radiation Oncology, has an established, world-leading graduate training programme for science graduates and clinical research fellows. This programme is a critical element in the drive to revolutionise radiation oncology and cancer research in the UK, to make advances in radiation biology, and to translate these into improved clinical outcomes for cancer patients. The training programmes are recognised internationally and attract the highest quality students and postdoctoral researchers. As such, they play a key role in training future leaders in oncology and radiobiology research, and contribute substantially to the UK requirements for important disciplines of cancer research.

Graduate Students

Our four year DPhil in Oncology programme has an annual intake of approximately 24 students. We have studentships funded by Cancer Research UK, the MRC, Oxford’s prestigious Clarendon Fund, and a number of joint scholarships with Oxford colleges. We also attract a large number of externally-funded students with Commonwealth or Government funding, or with Rhodes, National Institutes of Health (NIH) or Marshall Scholarships. We hope to increase these studentships as the Department continues to expand.

We offer our promising graduates a broad range of multidisciplinary and translational cancer research projects. As a result, our graduates come from a wide range of scientific backgrounds including biology, medicine, engineering, mathematics, chemistry and physics. By coming to the Department of Oncology they work alongside and learn from leaders in their field, and we provide them with a world-class academic environment and the best support services, including a comprehensive portfolio of personal and professional skills development.

The training programme continues at the postdoctoral level to help build capacity for cancer research both in Oxford and elsewhere, through training and retention of outstanding young scientists.

Group Leaders are responsible for the scientific training of postdoctoral researchers in their groups, including the identification of appropriate external courses. Postdoctoral researchers are encouraged to develop their supervisory skills by taking leading roles in the supervision of undergraduate or MSc student research projects. The senior postdoctoral researchers are also named DPhil student co-supervisors. In addition, we have established a formalised postdoctoral programme of mentoring and scientific and generic skills development training to enhance career opportunities for our postdoctoral staff.

Postdoctoral Researchers

Our established and successful MSc in Radiation Biology provides a core theoretical programme and also engages students in high quality basic and clinically-applied research. The MSc can be a stand-alone degree, although many of our MSc scholars are medical students intercalating the MSc before returning to their medical studies in the UK or overseas. Furthermore, the MSc can form the first year of graduate research training for both science and medical students, most of whom go on to complete the DPhil in Radiation Biology or a PhD elsewhere.

Our students are equipped with the scientific knowledge and cutting-edge technical skills to become the scholars, teachers and researchers for the next generation both in the UK and globally.

Clinical Research Training Fellows

Alongside our DPhil programme, we run an active and expanding Clinical Research Training Fellowship programme. It provides structured research training for medical graduates to obtain a DPhil degree in radiobiology-related research and also aids them in becoming successful clinicians and scientists.

Case Study

Monica Olcina del Molino. Originally from Spain, Monica joined the CRUK/MRC Oxford Institute for Radiation Oncology in 2009 from the University of Manchester with a first class degree in Pharmacy. She was in the first cohort of the MSc in Radiation Biology as part of an MRC-funded 4-year programme in Radiobiology. Monica obtained a distinction in her MSc in 2010 and then started her DPhil project in the laboratory of Ester Hammond. Monica’s research generated 5 publications on the effects of hypoxia and DNA damage in cancer research in high profile journals such as Cell Cycle, Molecular Cell and Clinical Cancer Research. During her DPhil, Monica’s research excellence was recognised through the successful attainment of an MRC Centenary Early Career Award, numerous travel awards and poster presentation prizes. Monica is now working as a postdoctoral researcher with Professor Annato Giaccia, Department of Radiation Oncology, Stanford University.

Peter O’Neill

Professor Peter O’Neill has been the Course Director of the MSc in Radiation Biology and Deputy Director of the CRUK/MRC Oxford Institute for Radiation Oncology within the Department of Oncology since 2005. He is a Fellow of the Royal Society of Chemistry. He was awarded the Fallow medal and the Weiss medal as an outstanding member of the scientific community in recognition of a history of significant contributions to radiation research.

Bledwyn Jones

Professor Bledwyn Jones is the Deputy Course Director of the MSc in Radiation Biology and researches on photon therapy at the CRUK/MRC Oxford Institute for Radiation Oncology within the Department of Oncology. He is clinically trained at the Guy’s Hospital and presently provides an advisory role in the CRUC. His work in Medical Physics and Clinical Radiobiology has been recognised by the award of Honorary Fellowship of the Institute for Physics and Engineering in Medicine and the award of Honorary Fellowship of the British Institute of Radiology.
communicating the impact of research

the department of oncology is committed to discovering new ways to reach the public and to support a culture of public engagement amongst its scientists.

our public engagement strategy rests on three pillars: our choice of audiences; collaboration with stakeholders; and highly interactive delivery.

the aims of our strategy are:

• to raise aspirations amongst future scientists and encourage post-16 study of science and maths
• to raise awareness of our work and the impact of our work amongst the general public and patient groups.
• to inform decision makers and opinion formers of our work
• to raise awareness of our work and the impact of our work amongst the general public and patient groups.
• to raise aspirations amongst future scientists and their teachers; patients, carers and allied health professionals; the general public; and high impact individuals.

the department of oncology as a major asset to the oxfordshire community.

our target audiences are broad: students in secondary education and their teachers; patients, carers and allied health professionals; the general public; and high impact individuals.

engaging with the public

as you might expect we are a firm feature of the local science festivals. during march each year we bring our science to the town centre events in oxford and abingdon and to wow!how? the university event in oxford’s museum of natural history. we also supported a festival to celebrate the centenary of the medical research council. these events help us reach large numbers of people and give scientists an opportunity to engage in short conversations with the public using existing engagement tools. the emphasis is very much on hands-on experience with table-top activities providing an interactive experience to support understanding amongst the visitors.

in addition, we have supported events further afield, including brighton science festival, big bang in birmingham and london, and the northeast science festival in newcastle.

our senior researchers regularly act as the keynote speakers for major fundraising events such as the cancer research uk race for life and relay for life.

we ask our scientists to engage others with their science. to support them we have developed a training course which helps them develop interactive tools for engagement and then provides an audience of school students and patients; interacting with this audience allows the scientist to gain confidence through a positive experience. feedback from the scientists has been very positive.

“it helps to make researchers enthusiastic about public engagement”

scientist participant on public engagement course

the resources developed during the course have been used at science festivals, and shared with other cancer research centres across the country. resources developed by our public engagement manager have been deposited with the times education supplement for use by teachers.

enhancing education

we have responded to numerous school requests for curriculum enrichment, reaching out across thames valley and further to sussex, durham, and denmark. we never just give talks, but have developed interactive workshops. our latest initiative is to work with students to develop public communications tools, an approach which culminated with our annual video competition, which began in 2013 in support of the mrc centenary; winning videos are published on youtube as the oxford cancer clips series.

“i really enjoyed making the video, and i learnt a lot while researching it. thank you for the opportunity to enter.”

year 12 student

our collaboration with the university of oxford’s outreach team has seen us deliver week-long oncology summer schools as part of the flagship unio program. we also deliver evening classes through collaboration with the university of oxford’s department for continuing education. these classes attract audiences as diverse as students, retired teachers, biotech employees and nhs trust workers.

forsaking aspirations to study science

at finding out that the students she had been interacting with were still at school - she thought they were graduate students. this is testament to the confidence and familiarity they displayed with the material that they had presented.

professor tim maughan addressing cruk race for life participants in oxford

mp andrew smith hears about our work during a visit to the department association to deliver sci-bar evenings at a local pub; with the university alumni relations office to reach the network of former students; and with the national cancer research institute (ncri) to develop their annual conference schools programme.

our collaborations gained us access to audiences that would have been hard to reach in any other way. we also collaborated with school students to produce new engagement resources. by working with our audience to produce something together, we have forged partnerships based on high levels of engagement, ingenuity and energy both in the creation of resources and in the presentation of science. one senior academic at newcastle reported shock

for more information about our research and details of publications, please go to www.oncology.ox.ac.uk for more information about our research and details of publications, please go to www.oncology.ox.ac.uk
treatment of cancer. These include understanding how normal tissue responses to radiation. The Institute aims to develop new treatments or combinations of treatments through the concepts of synthetic lethality and oncogenic vulnerability. It has established the infrastructure to deliver a wide portfolio of academic multi-centre early phase studies involving subsets of patients, and to perform detailed analyses of tumours before, during and after intervention to select patients.

Cancer Research UK and Engineering and Physical Sciences Research Council Cancer Imaging Centre in Oxford

Lead: Professors Ruth Muschel, Mike Brady and Gillies McKenna

The Cancer Imaging Centre in Oxford is one of four national Centres funded by a strategic initiative between CRUK and the EPSRC. Its establishment was headed by the CRUK/MRC Oxford Institute for Radiation Oncology to develop advanced image-based methods for use in cancer therapy, diagnosis and prognosis. Managed from within the Department of Oncology, it is built upon a University-wide and industrial consortium of imaging researchers and brings together multidisciplinary teams including radiologists, surgeons, radiation oncologists, medical oncologists, biologists, chemists, engineers and mathematicians. Together, through basic science, preclinical and clinical studies, they explore how imaging and image-analysis can be used to help select the most appropriate patients for treatment as well as how image-derived information can be used to guide treatment choices and direct assessment of response to therapy.

Department of Oncology Annual Grant Funding

CRUK/MRC 36%
CRUK/MRC, Oxford Institute for Radiation Oncology 33%
Other grants 31%
Centres* 6%

*CRUK, Oxford Centre, CRUK & EPSRC Cancer Imaging Centre in Oxford, NIHR Oxford BRC, Oxford ECMC

Cancer Research UK Oxford Centre

Director: Professor Gillies McKenna
Deputy Director: Professor Mark Middleton

The CRUK/MRC Oxford Institute for Radiation Oncology took a leading role in establishing the CRUK Oxford Centre in 2010 as a partnership between the University of Oxford, Oxford University Hospitals NHS Trust and Cancer Research UK. The Centre draws on the breadth and depth of fundamental research being undertaken at the University of Oxford and translates it into novel therapeutic strategies which increase cancer cure rates to save and improve people’s lives. The Centre currently comprises over 500 members from more than 25 Departments, Units and Institutes of the University, including the Department of Oncology. From where it is managed, as well as from the NHS Trust. Members work across a range of disciplines and collaborate on a local, national and international scale. The Centre supports the translation of novel ideas and hypotheses into early phase clinical trials to speed up the transition from scientific discovery to treatments in patients.

National Institute for Health Research Oxford Biomedical Research Centre

Director: Professor Keith Channon

The NIHR Oxford Biomedical Research Centre (BRC) brings together the research expertise of the University of Oxford and the clinical skills of the Oxford University Hospitals NHS Trust to support translational research and innovation to improve healthcare for patients. It is made up of 14 research themes covering all areas of therapy. The Cancer Theme, led by Department of Oncology Professors Mark Middleton and Adrian Harris, aims to develop new treatments or combinations of treatments through the concepts of synthetic lethality and oncogenic vulnerability. It has established the infrastructure to deliver a wide portfolio of academic multi-centre early phase studies involving subsets of patients, and to perform detailed analyses of tumours before, during and after intervention to select patients.

Oxford Experimental Cancer Medicine Centre

Lead: Professor Mark Middleton

The Oxford Experimental Cancer Medicine Centre (ECMC) is jointly supported by CRUK and the UK Department of Health. The goal of the ECMC initiative is to develop new therapies to bring benefits to patients faster. In Oxford the focus has been on the application of basic scientific discoveries in cancer biology to the development of novel therapies and prognostic/diagnostic biomarkers to help personalised patient care. Through a team of scientists based in the Department of Oncology, the Oxford ECMC has expertise in immunology, DNA repair, angiogenesis and molecular pathology and has facilities for conducting imaging, proteomics, microarray and radiobiology studies.

Oxford University Hospitals NHS Trust

The Churchill Hospital, part of the Oxford University Hospitals NHS Trust, is a world-renowned centre of excellence for cancer services and a major centre for healthcare research. The Cancer and Haematology Centre was opened in the Churchill Hospital in 2009, and brought together a wide range of medical and surgical services including cancer medicine, surgery, and diagnostic services. It serves as a base for University research teams, working in partnership with NHS colleagues. The Department of Oncology works closely with the Radiotherapy Department to ensure that research is rapidly and efficiently translated into cutting-edge clinical treatment for cancer patients. Through these partnerships, the use of Image-Guided Radiotherapy is widespread and the use of Intensity Modulated and Stereotactic Body Radiotherapy is increasing.

Working in Partnership

Providing a collaborative and nurturing environment for translational multidisciplinary cancer research is at the heart of the Department of Oncology. It is through these partnerships that we can attract long-term funding to remain at the forefront of oncology research. Furthermore, we work proactively within these partnerships on outreach and engagement with local schools, patient groups and the public to inform, educate and inspire.

Cancer Research UK and Medical Research Council Oxford Institute for Radiation Oncology

Director: Professor Gillies McKenna
Deputy Directors: Professors Tim Maughan, Ruth Muschel and Peter O’Neill

The Joint CRUK and MRC funded Oxford Institute for Radiation Oncology is an integral part of the Department of Oncology and is dedicated to exploring aspects of radiation biology, research that could yield new advances in the treatment of cancer. These include understanding how cells respond to and repair radiation-induced DNA damage, defining the microenvironmental factors that affect these responses and identifying targets to alter tumour or normal tissue responses to radiation. The Institute aims to integrate basic research with imaging science to advance radiation treatments. Incorporating these developments with radiotherapy in clinical trials allows identification of opportunities which have the potential to improve patient care and allow earlier detection of primary and metastatic cancers.

For more information about our research and details of publications, please go to www.oncology.ox.ac.uk
A team of talented and dedicated individuals works together to provide a comprehensive and supportive infrastructure that underpins the outstanding research of the Department of Oncology.

Management of the Department is the responsibility of the Executive Committee, which comprises the Head of Department and up to eight senior academics and managers from the Operations and Strategic Projects groups.

Operations
Lead: Pamela Nieto, Head of Administration and Finance
Management of the Department’s operational and financial activities falls to the Operations Group, led by Pamela Nieto and supported by Claire Shingler, Operations Manager. Each functional unit delivers activities in its dedicated area to ensure the smooth running of this large research intensive department. Specialist areas include HR, finance, facilities and health and safety, graduate studies, research facilitation, information technology and public engagement. Personal and Executive Assistants provide administrative support to the senior researchers, clinicians and their groups and play a vital role in the organisation of meetings, events and seminar series and in the support of department-wide activities. This strong and dedicated support base affords the added value of releasing senior scientific and clinical staff from the daily administrative tasks required to maintain excellence in the Department.

Human Resources
Lead: Claire Matthews, HR Manager
The HR team provides operational management, advice and guidance to managers and staff on all employment-related matters, such as recruitment, policy guidance, legislation and best practice. It runs a successful personal development review process for all staff in the Department and plays a key role in Athena SWAN activities.

Finance
Lead: Paul Godden, Strategic Finance Manager
The Finance team provides a wide-ranging service to the Department, which covers all areas of pre- and post-award management, procurement and finance. It offers particular expertise in the financial management of clinical trials. The team supports the Head of Department and Head of Administration and Finance with the management of the Department’s budget and works closely with senior scientific and clinical staff to cost new research proposals and administer internal and external grant awards.

Building and Facilities
Lead: Larry Turner, Building and Facilities Manager
The Building and Facilities team provides comprehensive research laboratory and facilities support across the Department. This includes routine and specialist services provision and day-to-day frontline support. The team manages a broad portfolio of equipment service contracts, develops service provisions and plays an active role in equipment procurement. It coordinates bespoke and specialist projects such as space reconfigurations and building refurbishment works. Larry Turner is the Departmental Safety Officer, providing guidance and advice on local and University-wide procedures and best practice.

Research Facilitation
Lead: Sarah Norman, Training and Development Lead
The Research Facilitation team is a first point of contact for external funding applications. It works with a wide range of scientists and clinicians from early career and postdoctoral researchers to senior academics and professors. The team contributes to the ongoing support for research in the Department, and the input and advice provided assists in preparing the highest quality funding applications.

Graduate Studies
Lead: Sarah Norman, Training and Development Lead
The Graduate Studies team works to ensure that all MSc, MRes and DPhil students are supported and developed throughout the course of their studies in the Department. The team also facilitates the admissions process and manages all student funding. It runs a comprehensive graduate training programme and organises careers events and a highly successful annual Student Symposium.

Information Technology
Lead: Claire Shingler, Operations Manager
Our team of IT professionals provides local desktop, server and database support to staff and students, in conjunction with Divisional and University IT staff. The team supports a mixed Mac and PC environment, manages a range of IT-related projects and provides assistance with the Department’s peripherals, mobile devices and other equipment.

Public Engagement
Lead: Martin Christlieb, Public Engagement and Communications Manager
Communicating the impact of our research is a key activity in the Department. Assisted by numerous research staff and students from a range of disciplines, our Public Engagement Manager educates and inspires school students, teachers, patients, the general public and scientists alike. This is done through a variety of ways, including lab tours, school visits, science festivals and adult education courses.

Strategic Projects
Lead: Claire Bloomfield, Strategic Projects Manager
The Strategic Projects Group works closely with the Head of Department to take forward key initiatives of strategic importance to the Department. Examples of their work include large funding bids and the establishment of new research facilities. Specialist Project Managers oversee the CRUK Oxford Centre, the BRC Cancer Theme, Experimental Cancer Medicine Centre and the CRUK & EPSRC Cancer Imaging Centre in Oxford.
For more information about our research and details of publications, please go to www.oncology.ox.ac.uk