CRUK/MRC Oxford Institute for Radiation Oncology
Contents

Message from Professor Gillies McKenna, Director of Institute 2

Introduction 3

DNA Damage and Repair 4

Tumour Microenvironment 14

Clinical and Translational Research 24

Scientific Cores and Specialist Facilities 38

Training 48

Communicating the Impact of Research 50

Working in Partnership 52

Running the Institute 54

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For more information about our research and details of publications, please go to www.radiationoncology.ox.ac.uk
Message from Professor Gillies McKenna, Director of Institute

It is with great pleasure, as Director of the Cancer Research UK and Medical Research Council Oxford Institute for Radiation Oncology, that I introduce this brochure and share with you the highlights of our work. We have developed and grown enormously over the past few years, firmly establishing radiation oncology as a major research field within the UK for the 21st Century.

Our mission at the Institute remains, as ever, to be a world-class centre for radiation biology research through exploration of aspects of radiation biology that could yield new advances in the treatment of cancer.

I am proud to say that we are achieving this mission and fulfilling our aims: to understand how cells respond to and repair radiation-induced DNA damage, to define the microenvironmental factors that affect these responses, to identify targets to alter tumour or normal tissue responses to radiation, and to facilitate rapid translation from scientific discovery to patient benefit. In support of all of these areas, we are focused on improving tumour imaging, particularly for the detection of metastatic disease.

To realise success, it is essential 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, together with the Department of Oncology, 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, therefore, worked hard to form close and lasting partnerships across Oxford. Thanks to the initiatives that we have led, such as the CRUK/Oxford Centre and the CRUK EPSRC Oxford Imaging Centre, we have seen huge advances, to name but a few, in determining potential molecular agents to improve efficacy of treatment, in applying imaging methods for easier detection of metastases and in 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 aspire to be a world-class leader in taking fundamental research ideas through to early phase radiation therapy clinical trials and, ultimately, through to improvements in patient outcome. This can only be realised with superb underpinning infrastructure and strong links to other UK research centres.

We pride ourselves on supporting and training the next generation of world leaders in cancer research to ensure our privileged position to have a great wealth of broad-ranging expertise and a powerful network of cancer researchers. We have, therefore, worked hard to form close and lasting partnerships across Oxford. Thanks to the initiatives that we have led, such as the CRUK/Oxford Centre and the CRUK EPSRC Oxford Imaging Centre, we have seen huge advances, to name but a few, in determining potential molecular agents to improve efficacy of treatment, in applying imaging methods for easier detection of metastases and in 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 aspire to be a world-class leader in taking fundamental research ideas through to early phase radiation therapy clinical trials and, ultimately, through to improvements in patient outcome. This can only be realised with superb underpinning infrastructure and strong links to other UK research centres.

We see the next decade as one where this integration and collaboration will enable huge strides in the enhancement of radiotherapy treatment and changes in clinical practice, leading to increased survival rates in the UK.

I hope you enjoy reading more about the Institute, our people and the depth and breadth of the activities we support.

Gillies McKenna

Professor Gillies McKenna
Director of CRUK/MRC Oxford Institute for Radiation Oncology

Introduction

Welcome to the CRUK/MRC Oxford Institute for Radiation Oncology brochure. The past few years of the Institute’s history have been exciting and eventful; we have seen the birth of large collaborative cancer research and cancer imaging networks, expanded our research and clinical trial activities and made important scientific discoveries.

A centre of excellence for radiation research

The Institute was formed in 2005 (then named the Gray Institute for Radiation Oncology and Biology) through a partnership between the University of Oxford, Cancer Research UK (CRUK) and the Medical Research Council (MRC). The creation of this much-needed international centre of excellence in radiobiology research was fuelled by the need to address both the decline of radiation biology research in the UK and the quality of radiotherapy provision that was contributing to poor survival rates of cancer patients.

As one of the world-leading centres dedicated to radiation oncology and biology, the Institute now houses over 200 staff and postgraduate students - both clinical and non-clinical - and brings together research and clinical groups from a range of disciplines, including biology, chemistry, physics, medicine and computational biology. The Institute is funded by an annual £10M core grant from CRUK and MRC, which supports research groups based in the Old Road Campus Research Building, the Radiobiology Research Institute and the NHS Cancer and Haematology Centre. Significant effort is being put into expanding radiotherapy clinical trials activity.

The CRUK/MRC Oxford Institute for Radiation Oncology’s Main Funders

Supporting research

Our main research themes of DNA damage 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 utilise local expertise in neighbouring University facilities such as the Target Discovery Institute.

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

Working and studying with us

We are committed to maintaining organisational and cultural practices that promote gender equality, and to improving the working environment for all. The personal and career development of our students and staff is very important to us and we are working hard to ensure that our most talented researchers, both men and women, are supported to become the future leaders in their fields.

In conjunction with the Department of Oncology, we have embedded into our culture an annual Personal Development Review process for all staff and a mentoring programme for our postdoctoral researchers and group leaders. We also have a postdoctoral network and run a busy programme of seminars with speakers invited from around the world. Our postgraduate students are provided with a world-class academic environment and the best support services, including a comprehensive portfolio of personal and professional skills development.

In recognition of our efforts, the Department of Oncology was awarded a departmental Athena SWAN Bronze award in July 2014 and we are now working towards gaining a Silver award.

Athena SWAN Bronze Award

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

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DNA contains the critical genetic information in all living cells. When cells grow and divide they need to correctly replicate their DNA and to 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 focusses 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.

DNA interstrand crosslinks (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 the Institute 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
Institute 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.

Research in the Institute 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.

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, and replication, and by chromosome structure, chromatin and telomeres. Failure of these responses causes genomic instability and cancer.

Research at the CRUK/MRC Oxford Institute for Radiation Oncology 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.

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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 DiSo), and have been used in companion diagnostics.

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 QIAGEN 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 resides) 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 deoxyribonucleotides (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).

Figure 1: Cullin-Ring ubiquitin Ligases (CRLs) are multisubunit E3 enzymes: This figure presents the assembly of a prototypical multisubunit E3 through adaptors. Substrates contain a domain that serves as a signalling platform for the recruitment by the E3. RBX1/2 are recruited by cullins to bridge the substrate selected by the substrate recognition protein to the E2. E2 and E3 provide activated ubiquitin molecules that are coupled with target lysine residues within the substrates. Poly-ubiquitinated substrates are degraded by the proteasome. NAE (Neddy1-activating enzyme) catalyses the transfer of NEDD8 to cullins. Chemical approaches to target the UPS are outlined. Figure published in British Journal of Cancer 9 December 2014 doi:10.1038/bjc.2014.594

Chemical approaches to modulate the UPS

Proteasome inhibitor (Bortezomib)

NAE inhibitor (MLN4924)

Rbx1/2

Ub

Activator/Inhibitor of substrate recognition

Nedd8

Ub

Substrate

Adaptor

Multi-subunit Cullin-Ring ubiquitin Ligase E3

NEDD8

Ub

Cullin

Substrate

We synthesise cyclic mini-DNA duplexes to facilitate the study of base pairing in DNA (including mutagenic lesions) at high resolution.

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 blockade 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.

Vincenzo D’Angiolella

Vincenzo D’Angiolella is an MRC Group Leader at the CRUK/MRC Oxford Institute for Radiation Oncology. He has a Medical Degree (MD) from the University of Naples “Federico II” and completed his PhD at the same University in the field of General Pathology. Following the completion of his studies, he worked as a postdoctoral fellow at the New York University School of Medicine in the USA in the laboratory of Dr Michele Pagano. He has been awarded fellowships from AIRC (Associazione Italiana per la Ricerca sul Cancro) and AICF (American Italian Cancer Foundation) and was a Scholar of the Leukemia & Lymphoma Society from 2008 to 2011.

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Tom Brown

Tom Brown came from Southampton to Oxford University in 2013 to take up a joint Chemistry/Oncology position as Professor of Nucleic Acid Chemistry. He has published over 300 scientific papers and patents and has received several awards including the Royal Society of Chemistry awards for nucleic acid chemistry and for interdisciplinary research. He is President of the Chemistry Biology Interface Division of the Royal Society of Chemistry, co-founder of CRUK/MRC Oxford Institute for Radiation Oncology. He has a Medical Degree (MD) from the University of Naples “Federico II” and completed his PhD at the same University in the field of General Pathology. Following the completion of his studies, he worked as a postdoctoral fellow at the New York University School of Medicine in the USA in the laboratory of Dr Michele Pagano. He has been awarded fellowships from AIRC (Associazione Italiana per la Ricerca sul Cancro) and AICF (American Italian Cancer Foundation) and was a Scholar of the Leukemia & Lymphoma Society from 2008 to 2011.
Biochemistry and Regulation of DNA Repair Group

The long-term goal of our work is to study the proteins and mechanisms involved in 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 also plays a role in repair of DNA damage induced by radiation and 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.

Chromosome Integrity Group

The aim of our research is to understand how genome stability is maintained in response to DNA double-strand breaks.

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.radiationoncology.ox.ac.uk
DNA Damage and Repair

**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 radiosensitizer 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 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.

**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 the 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 an evolutionarily conserved segregase that with the help of specific cofactors binds and remodels (segregates) diverse and most 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-associated 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 hepatobucarillary carcinoma (Figure 2; green arrow indicates tumour mass) that is caused by mutations in p97-cofactor SPRTN (Figure 3; genomic localisation and protein structure of SPRTN with patient mutations).

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.
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). The breast cancer-associated gene BRCA2 is one such example. 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 tumorigenesis. 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.

Figure 1: Accumulation of homologous recombination proteins RAD51 and RAD51C into sub-nuclear foci in response to ionising radiation.

Figure 2: Chromosome breakage in human cancer cells lacking BRCA2 gene (arrows indicate breaks).

Figure 3: Dysfunctional telomeres (green) are recognised as damaged DNA (red) and can initiate cancer.
Tumour Microenvironment

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, allowing 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 at the CRUK/MRC Oxford Institute for Radiation Oncology are investigating the tumour microenvironment in a number of ways. Work is underway to better understand signalling pathways within the cell and how alteration of these pathways can influence cancer onset and therapy and ultimately lead to personalised medicine approaches. 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. 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 secondary cancer (metastasis). Work is ongoing to advance and apply imaging methods using novel imaging agents for earlier detection of metastases. In related work, the impact of microenvironmental factors on the effectiveness of treatment is being investigated with a view to identifying new therapeutic targets. 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 Institute is overcoming resistance to radiotherapy. Programmes are underway to investigate the molecular mechanisms that contribute to radiation survival and to target these mechanisms to make tumour cells more responsive to radiotherapy. An example is the study of hypoxia (regions of low oxygen), which is common in tumours and often associated with poor treatment outcome, both with chemotherapy and radiotherapy. As such, hypoxia provides a target for cancer therapy. This is the subject of investigation, both by finding ways of making tumours less hypoxic during radiation therapy and by identifying drugs that target specifically hypoxic regions of tumours, which may be highly effective in combination with radiotherapy. Hypoxia is also being targeted by developing novel therapeutic agents that only work in the absence of oxygen. Technologies are being advanced for visualisation of changes in tumour microenvironment which will allow response to therapy to be monitored.

Metabolism and immunity in the detection and treatment of cancer

Cancer researchers are becoming increasingly interested in metabolism and the immune response. Altered metabolism is one of the hallmarks of cancer and as such, metabolic imaging has the potential to revolutionise the diagnosis and management of cancer. The immune system plays multiple roles in cancer; some cancers and treatments may weaken immunity, but the immune system can also help to fight cancer. Our researchers are exploring the molecular mechanisms by which immune cell recruitment into primary tumours and distant organs can mediate escape from anticancer treatments. They are also working to gain a better understanding of the effect of conventional treatments on the tumour microenvironment and inflammatory responses in cancer.
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 repair defect 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 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.

In order to progress beyond a certain size, tumours need to develop their own blood supply for nutrients and oxygen.

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.

Ester Hammond

Ester Hammond is a CRUK Group Leader and Associate Professor at the CRUK/MRC Oxford Institute for Radiation Oncology. She completed her PhD at the School for Cancer Sciences, University of Birmingham then accepted a post as a postdoctoral fellow within the Molecular Oncology Group at the University of Cambridge School of Clinical Medicine. Subsequently, she moved to the USA to join the Department of Radiation Oncology at Stanford University, first as a postdoctoral fellow then a research associate. She joined the Oxford Institute in 2007 as a CRUK group leader. Ester was awarded the 2015 Michael Fry Research Award from the North American Radiation Research Society.
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-PLK1-PTEN-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 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.

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 tumour vascularity or so-called vascular normalisation, and strategies to reduce tumoural 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.

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

Our lab has focused on the RAS effector RASSF1, which is significantly inactivated by CpG island methylation in all major solid tumours. Epigenetic silencing of the RASSF1 promoter not only associates with tumour onset but also affects prognosis and is being adopted as a potential predictive biomarker for treatment in certain cancers. We have concentrated on uncovering the role for RASSFs in normal biology to understand why loss of expression has such widespread association with cancer initiation. Through this approach we have found that RASSF1A plays a key role in governing control of the hippo stem cell pathway and is important for genomic protection via the familial breast cancer tumour suppressor gene, BRCA2.

We are continuing to look at both these aspects with the intention of highlighting intervention strategies that are biologically relevant to patients with RASSF1 methylation, alongside developing plasma-based detection methods for this epigenetic event. We are collaborating with projects in lung, breast and colorectal susceptibility where RASSF1A methylation has a poor prognosis and are working together with clinicians and developmental biologists on the role of selective stem cell regulation in the onset of gliomas.

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 can 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 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 radiotherapy 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.

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

With regards to bioavailability, a significant hurdle is the presence of the blood-brain barrier (BBB). We have recently shown that it is possible to make the BBB selectively leaky at sites of brain metastasis, and that this approach enables metastasis-targeted delivery of both diagnostic agents and relevant therapies (Fig. 2).

The above ongoing studies feed into our overall research programme, in which our primary aims are to (1) determine the role of inflammatory processes in brain metastasis development and response to radiotherapy, and (2) develop novel approaches to imaging the tumour microenvironment for early diagnosis and treatment monitoring.

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.

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.

Nicola Sibson

Nicola Sibson is Professor of Imaging Neuroscience, CRUK Group Leader and Director of Graduate Studies at the CRUK/MRC Oxford Institute for Radiation Oncology. On completion of her PhD at the University of Cambridge, Nicola spent four years at Yale University, before joining the MRC Biochemical and Clinical Magnetic Resonance Unit in Oxford. Subsequently, she moved to the Department of Physiology, Anatomy and Genetics as a University Research Lecturer, and was recruited to the Institute in 2007. Nicola has given numerous plenary lectures at national and international meetings, including the prestigious British Neuropathological Society Lecture, at the Neuro-Oncology Society Annual Conference, and serves on many funding panels and advisory boards. Nicola was recently made a Special Supernumerary Fellow of University College Oxford.
A key aim of the CRUK/MRC Oxford Institute for Radiation 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 the Institute 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 Institute 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 Institute’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 of Oncology’s Early Phase Clinical Trials Unit (EPCTU) and Oncology Clinical Trials Office (OCTO), which together, provide the necessary infrastructure and expertise to set up and run studies in Oxford and throughout Europe.
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 chemo-radiotherapy 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.

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 radiation biology, 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 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.

For more information about our research and details of publications, please go to www.radiationoncology.ox.ac.uk
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 chemotherapy 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 desmoplastic tumour microenvironment and the inflammatory and immune response, as the immunosuppressive desmoplastic 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 SCALOP trial and co-lead for radiotherapy for the ESPAC5F trial, Somnath has already influenced national practice by introducing chemoradiation 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/radiosistance, hypoxia, development of peripheral blood biomarkers/circulating tumour DNA for radiation response and novel imaging for early detection of radiation response/resistance.

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), radiotherapy 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 explore 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 then be 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 (in oesophageal cancer) and 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 delivery technique in patients receiving combined chemoradiation and surgery.
Clinical and Translational Research

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 sRNA 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 radiotherapy.

We are also interested in finding innovative ways of reversing tumour hypoxia which reduces radiosensitivity 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.

Figure 1: 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.

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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 Institute’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 (‘Foxfire’) 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 PI3kinase-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 FOCUS 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.

For more information about our research and details of publications, please go to www.radiationoncology.ox.ac.uk
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. Radiotherapy 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. Radiotherapy 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 and/or diffusion properties in tissue, telling us about oxygen supply. PET can be used to map glucose metabolism using position emitting radionuclides such as fluorine-18 labeled fluorodeoxyglucose (18F-FDG) and hypoxia using fluoromisonidazole (18F-FMISO).

Radiotherapy treatment plan for an oesophageal cancer patient, showing the potential for dose escalation to the tumour.

Entire volume treated to 50 Gy. (outer red contour)
Tumour boosted to 62.5 Gy. (inner red contour)

Figure produced in collaboration with Dr Samantha Warren and Dr Maria Hawkins.

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-FMISO and 18F-FDG 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.

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, oxaplatin and folinic acid) with chemotherapy plus radioembolisation for colorectal cancer that has spread to the liver: Radioembolisation (also called selective internal radiotherapy or SIRT) delivers radioactivity 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, nelfinavir, 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).

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

**Mike Partridge**

Mike Partridge is an Associate Professor and has been a CRUK Group Leader of the Radiotherapy Physics Research Group at the CRUK/MRC Oxford Institute for Radiation Oncology within the Department of Oncology since 2012. He is a Fellow of the Institute of Physics. He has been working in medical imaging and radiotherapy research since 1999. He studied Natural Sciences at Cambridge University before working as a postdoctoral scientist at the Institute of Cancer Research and The Royal Marsden Hospital in London, and at the German Cancer Research Centre in Heidelberg.

**Ricky Sharma**

Ricky Sharma has been an Associate Professor and Group Leader of the Translational Biomarker Development Group at the CRUK/MRC Oxford Institute for Radiation Oncology in the Department of Oncology since 2007. He is also an Honorary Consultant in Clinical Oncology at the Oxford University Hospitals NHS Trust and a Senior Research Fellow at Harris Manchester College, University of Oxford. He is a Fellow of both the Royal College of Physicians and the Royal College of Radiologists. He co-chairs the Early Phase Trials Workstream of the NCRI Clinical Translational Radiotherapy ICTRI Group and is the founding chair of the Cancer Teaching Committee, University of Oxford.
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 signal 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, and 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 (OxCoD), we are investigating radionanoparticles, 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 alpha particles or low energy particles, such as Auger electrons.

We use a combination of novel autoradiography approaches and Monte Carlo modelling 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.

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, alpha 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 imaging 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.radiationoncology.ox.ac.uk
Advanced Technology Development Group

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 CRUK/MRC Oxford Institute for Radiation Oncology offers a number of world-leading scientific cores and specialist facilities, which 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.

Researchers at the Institute have full access to all the core facilities within the Department of Oncology. The strength of these 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.

Expertise in the facilities 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. The facilities provide imaging at the cellular and whole body level using advanced microscopy techniques and multiple imaging platforms, including MRI, and they also offer 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, our researchers and clinicians have access to expertise in clinical trial design, optimisation and management as well as our key areas of focus in cancer research: DNA damage and repair, tumour microenvironment and clinical and translational research. A number of new facilities have been created across the Institute and the Department of Oncology since 2014.

The Microscopy Core has been successful in consolidating state-of-the-art equipment and providing dedicated and 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

Biomedical Oncology Clinical Trials Office
CLINICAL IMAGING PET Radiochemistry
Clinical Radiotherapy DNA Damage & Repair Preclinical Imaging
Bioanalysis Tumour Microenvironment
Clinical & Translational GCP LABS Preclinical Validation
Radiation Physics Early Phase Clinical Trials Unit
Microscopy Preclinical Imaging

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 Institute and provide comprehensive support for
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 intimate 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 GLCP 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 *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 Radiotherapy 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.

For more information about our research and details of publications, please go to www.radiationoncology.ox.ac.uk
Scientific Cores and Specialist Facilities

**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 training 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 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 radiation 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.
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-speed multidimensional imaging for researchers investigating processes at the cellular level. Fluorescently-labelled proteins can be visualised to provide an insight into their location and function in both fixed and living cells. We provide advice on sample preparation, labelling, imaging techniques and image processing.

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.

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 academic groups in the UK, Europe, USA and Australia we have recruited over 10,000 patients into trials.

We work with academic 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.

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 radiochemistry 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 PET imaging agents for trials and develop, validate and manufacture new tracer candidates.

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.

Images courtesy L.Bradley, N.Vlahov and B.Markelc.
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.

Localisation of DNA repair proteins (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.
Oxford’s prestigious Clarendon Fund, and a number of joint studentships funded by Cancer Research UK, the MRC, Our four year DPhil in Radiation Biology programme has attracted the highest quality students and postdoctoral researchers. As such, they play a key role in training future leaders in radiation biology, and contribute substantially to research into improved clinical outcomes for cancer patients. The training programmes are recognised internationally and attract the highest quality students and postdoctoral research fellows. This programme is a critical element in the drive to revolutionise radiation oncology research in the UK and globally. 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.

Postdoctoral Researchers
Our training programme continues at the postdoctoral level to help build capacity for radiation research both in Oxford and elsewhere, through training and retention of outstanding young scientists willing to devote their careers to the radiation sciences.

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.

Case Study
Tracy Underwood. Tracy graduated with a BSc in Physics from the University of Oxford and an MSc in Medical Engineering and Physics from King’s College London. She then joined the CRUK/MRC Oxford Institute for Radiation Oncology to pursue an MRC-funded DPhil project on the dosimetry of small photon beams, supervised by Mark Hill, Helen Winter and John Fenwick. To date, the key paper from Tracy’s DPhil research (published in Physics in Medicine and Biology) has been downloaded over 11,000 times. Her work also prompted a leading commercial dosimeter manufacturer to prototype a new water-equivalent detector for small photon beams: the DiodeAir. After submitting her DPhil thesis, Tracy received an MRC Centenary Early Career Award and was the 2015 winner of the IET/ImechE prize for the Best Medical Engineering PhD. Tracy is currently a Marie Curie Research Fellow with a joint appointment at Harvard Medical School and University College London.

Training the next generation of scientists and clinicians to become leaders in cancer research is central to the CRUK/MRC Oxford Institute for Radiation Oncology’s mission.

The Institute 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 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 radiation biology, and contribute substantially to the UK requirements for this important discipline of cancer research.

Graduate Students
Our four year DPhil in Radiation Biology programme has an annual intake of approximately 20 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-Nilri or Marshall Scholarships. We hope to increase these studentships as the Institute and the Department of Oncology continue 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 Institute 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.

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

Case Study
Tracy Underwood. Tracy graduated with a BSc in Physics from the University of Oxford and an MSc in Medical Engineering and Physics from King’s College London. She then joined the CRUK/MRC Oxford Institute for Radiation Oncology to pursue an MRC-funded DPhil project on the dosimetry of small photon beams, supervised by Mark Hill, Helen Winter and John Fenwick. To date, the key paper from Tracy’s DPhil research (published in Physics in Medicine and Biology) has been downloaded over 11,000 times. Her work also prompted a leading commercial dosimeter manufacturer to prototype a new water-equivalent detector for small photon beams: the DiodeAir. After submitting her DPhil thesis, Tracy received an MRC Centenary Early Career Award and was the 2015 winner of the IET/ImechE prize for the Best Medical Engineering PhD. Tracy is currently a Marie Curie Research Fellow with a joint appointment at Harvard Medical School and University College London.

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 Taita medal and the Weiss medal as an outstanding member of the scientific community in recognition of a history of significant contributions to radiation research.

Bleddyn Jones
Professor Bleddyn Jones is the Deputy Course Director of the MSc in Radiation Biology and researcher 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 Group of Hospitals and currently provides an advisory role in the clinic. 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 CRUK/MRC Oxford Institute for Radiation 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, and to help them see the Institute as a major asset to the Oxfordshire community.
- To inform decision makers and opinion formers of the impact of our work, and to help them see the Institute 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!"

Scientists 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 Cips 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 UNIQ 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.

Forging Partnerships

Local patient support groups are an important target audience and our update sessions focused on current research have been well received, providing hope and information to those who attend.

"My wife and I found [the evening] informative and encouraging. Keep up the good work to conquer cancer!"

Member of patient group

We reach out to local VIPs especially those who can act as ambassadors for our work or who have influence or make decisions. Our guests have included the local MP, Andrew Smith, members of the county council, and the Lord Lieutenant of Oxfordshire.

Collaboration is key to good science and also good engagement. We joined hands with the British science association to deliver SciBar 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 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.

For more information about our research and details of publications, please go to www.radiationoncology.ox.ac.uk
Maximise opportunities for future improvements in the treatment and detection of cancer. Work in the Department is multidisciplinary and focuses on the main research themes of DNA damage and repair, tumour microenvironment and clinical and translational research. Combining expertise in basic research and clinical trials allows identification of opportunities which have the potential to improve patient care and increase cancer cure rates. The Institute is housed within the Department of Oncology.

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 aims to draw on the breadth and depth of fundamental research being undertaken at the University of Oxford and translate it into novel therapeutic strategies which increase cancer cure rates and 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 Institute, the Department of Oncology, as well as from the NHS Trust. Members work across a range of disciplines and collaborate on a local, national and international scale.

The Department of Oncology was formed in 2010 with Head of Department: Professor Gillies McKenna

Department of Oncology
Head of Department: Professor Gillies McKenna

The Department of Oncology was formed in 2010 with the vision of enhancing basic and clinical cancer research in Oxford. It was born out of a collective desire amongst senior leaders in Oxford and major funders to create a structure for cancer research in Oxford that would maximise opportunities for future improvements and investments in the service of improving cancer care.

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 diagnostic biomarkers to help personalise patient care. Through a team of scientists and clinicians led by Professor Mark Middleton, the Oxford ECMC has expertise in immunology, DNA repair, angiogenesis and molecular pathology and has facilities for conducting imaging, proteomics, microarray and radiosotope 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.

Working in Partnership

Providing a collaborative and nurturing environment for translational multidisciplinary cancer research is at the heart of the CRUK/MRC Oxford Institute for Radiation Oncology. It is through these partnerships and international collaborations 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.

Department of Oncology Annual Grant Funding

CRUK/MRC Oxford Institute for Radiation Oncology

Other grants

36%

33%

33%

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

For more information about our research and details of publications, please go to www.radiationoncology.ox.ac.uk
Management of the Institute is the responsibility of the Executive Committee, which comprises the Institute Director 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 Institute’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 institute. 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 institute-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 Institute.

**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. The team runs a successful personal development review process for all staff in the Institute 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 Institute, which covers all areas of pre- and post-award management, procurement and finance. The team offers particular expertise in the financial management of clinical trials. It supports the Institute Director 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 Institute. 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.

**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 Institute. 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.

**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 Institute, and the input and advice provided assists in preparing the highest quality funding applications.

**Public Engagement**  
**Lead:** Martin Christlieb, Public Engagement and Communications Manager  
Communicating the impact of our research is a key activity in the Institute. 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 the Department of Oncology 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.

**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 Institute’s peripherals, mobile devices and other equipment.

A team of talented and dedicated individuals works together to provide a comprehensive and supportive infrastructure that underpins the outstanding research of the CRUK/MRC Oxford Institute for Radiation Oncology.
Contact Us

For more information on the CRUK/MRC Oxford Institute for Radiation Oncology, visit our website at: www.radiationoncology.ox.ac.uk
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