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Spotlight on Personalised Medicine





## Joint Annual Research Report 2009/10

The Royal Marsden NHS Foundation Trust and  
The Institute of Cancer Research

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## The Royal Marsden and The ICR – From Bench to Bedside

The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research work in partnership to produce high quality basic research and translational studies, with the aim of developing better treatments for the benefit of cancer patients worldwide.

We pursue excellence every step of the way, from meticulously designed bench experiments and clinical trials, to our level of bedside patient care when delivering new treatments.

### The Royal Marsden NHS Foundation Trust

- We are one of the world's leading cancer centres, specialising in the treatment and care of people with cancer as well as cancer diagnosis and research.
- With hospitals in Chelsea and Sutton, and a chemotherapy suite at Kingston Hospital we treat more than 40,000 patients from across the UK and abroad every year.
- We are a major provider of molecular diagnostics in the UK, allowing us to identify patients who would benefit from specific anti-cancer therapies and to tailor treatment programmes to the individual.
- Our clinical units are internationally renowned for conducting Phase I, II and III clinical trials.
- Our Drug Development Unit sees around 500 patients per year, over half of whom are treated on Phase I clinical trials, and makes an important contribution to the world-wide effort to discover and develop new drugs.
- In 2009, we achieved a rating of 'excellent' for quality of service and for the use of resources in the Care Quality Commission's Annual Health Check. We are the only Trust in the country to achieve the highest rating possible for nine consecutive years.

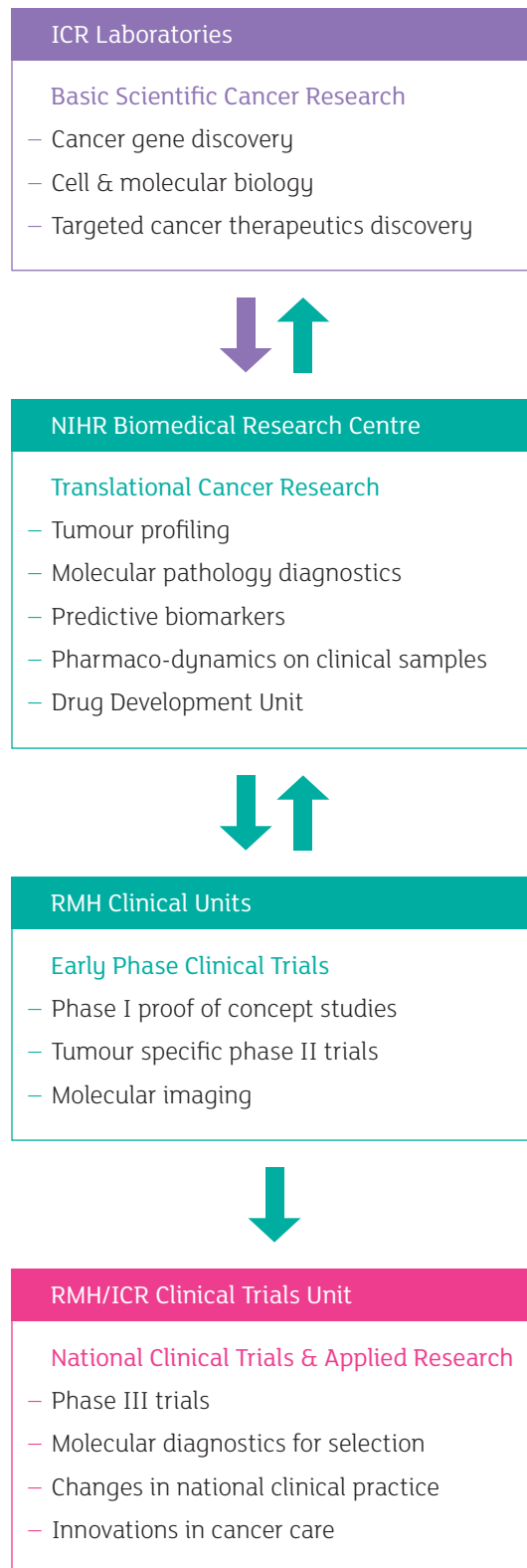
### The Institute of Cancer Research

- In 1909, the ICR was created as a small research department of The Royal Marsden. We are now one of the world's leading cancer research organisations.
- In December 2008, we were ranked the UK's top academic research centre by The Times Higher Education, in an authoritative interpretation of the 2008 Research Assessment Exercise (RAE). The RAE is the government's peer review analysis of research from UK universities.
- We made the important discovery that the basic cause of cancer is DNA damage, and have subsequently played a leading role in identifying genes involved in cancer.
- Our scientists are internationally renowned for cancer research and we are consistently the most effective Higher Education Institution (HEI) in the UK in terms of the impact on our scientific peers of our published work in biomedical sciences.
- We are a college of the University of London and in 2009, we have a total of 292 students enrolled to become the next generation of cancer researchers.

Together we form the largest comprehensive cancer centre in Europe. We were selected in 2006 as a National Institute for Health Research (NIHR) Biomedical Research Centre, specialising in cancer. We are planning new developments in Molecular Pathology, which aim to aid the translation of the leading-edge research conducted in the laboratories to improvements in patient outcomes.

**RMH/ICR Research Strategy**

The seamless transition from basic research to large-scale, practice-changing clinical trials.



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Mrs Tessa Green CBE

Chairman, The Royal Marsden.

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Professor Peter W J Rigby FRS FMedSci

Chief Executive, The Institute of Cancer Research.

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Lord Richard Ryder

Chairman, The Institute of Cancer Research.

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Miss Cally A Palmer CBE MSc MHSM DipHSM

Chief Executive, The Royal Marsden.



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## Review of 2009/10

### From the Chairmen and Chief Executives

We are very pleased to present our Joint Annual Research Report for 2009/10, which documents another year of notable achievements and significant progress in cancer research.

The Royal Marsden NHS Foundation Trust (The Royal Marsden) and The Institute of Cancer Research (ICR) together form the largest Comprehensive Cancer Centre in Europe, and one of the largest in the world. Our mission, to relieve human suffering by pursuing excellence in the fight against cancer, is pursued within a framework of activities in research and development, education and training, and the treatment and care of people affected by cancer.

Everything that we do is supported by the public, through their taxes and charitable donations, and is focused on benefiting cancer patients. It is therefore of the utmost importance that our work is of the highest international standard. Once again, the Higher Education Yearbook, produced by Evidence Ltd, reported that our published research papers had the greatest impact on our scientific peers of any Higher Education Institution in the United Kingdom. This is the sixth consecutive year in which we have led this ranking, which is a considerable tribute to the quality of our science. The Royal Marsden again achieved a double excellent rating, for quality of service and use of resources, from the Care Quality Commission, and is the only hospital in England to have achieved the best performance rating for nine consecutive years.

#### Key Achievements

We have continued to pursue our “bench to bedside and back again” strategy for cancer research. Last year we reported on a novel drug called olaparib, a poly (ADP-ribose) polymerase (PARP) inhibitor originally made by KuDOS Pharmaceuticals (now owned by AstraZeneca), that our scientists and clinicians had shown to exhibit great promise in Phase I trials. The

Phase II trials of this drug have now been reported and we continue to be extremely excited about its prospects for treating women with breast and ovarian cancer.

Prostate cancer is now the commonest cancer in men in the UK, so we have focused on developing multiple new treatments for this disease. Abiraterone acetate is a drug, made here in the early 1990s, in the forerunner of the Cancer Research UK Cancer Therapeutics Unit, which blocks the synthesis of the male sex hormone testosterone. Dr Johann de Bono has led its clinical development through Phase I and II trials in men with hormone-refractory prostate cancer, which showed enormous promise, and he has been the Co-Chief Investigator on the Phase III clinical trial, which was presented at the recent meeting of the European Society for Medical Oncology. This international trial involved almost 1200 men from 147 hospitals in 13 countries around the world, the largest Phase III clinical trial ever conducted in advanced prostate cancer patients, and has met its required endpoints by substantially improving overall survival in this population of patients. It is envisioned that these data will soon lead to a regulatory submission and we hope that abiraterone will be approved for widespread use for patients with

## Review of 2009/10 (continued)

From the Chairmen and Chief Executives

advanced prostate cancer. Finally, based on these exciting results, a clinical trial sponsored by Cancer Research UK is now underway to evaluate the utility of abiraterone in the treatment of patients with advanced breast cancer.

As reported last year, we are determined to improve the breadth and depth of our translational work, and to this end we appointed Professors Alan Ashworth and David Cunningham as Co-Directors of Research Integration. They have led the development of plans for the Centre for Molecular Pathology (CMP), a new building on our Sutton Campus, made possible by generous funding from the National Institute for Health Research (NIHR), the Wolfson Foundation and The Royal Marsden Cancer Charity. The CMP will exemplify our commitment to personalised medicine, also known as individualised, or stratified, treatment. The objective of personalised medicine is to precisely match the treatment given to the underlying genetic causes of a patient's tumour to achieve the best results for patients. The CMP will allow us to systematically collect tissue samples and to analyse them with modern, high-throughput approaches so that our clinicians can have the most complete molecular description of the underlying defect causing a cancer, when making decisions about optimum treatment. The CMP will also play a major role in the identification of new drug targets, through studies of tumour samples and an improved knowledge of how those tumours responded to treatment.

In June 2010 we were delighted to launch our Academic Partnership with the Mount Vernon Cancer Centre with the aim of integrating our research infrastructure and maximising the contribution all partner organisations make to better ways of diagnosing and treating cancer.

Our Director of Clinical Research and Development, Professor Stephen Johnston, leads the NIHR Specialist Biomedical Research Centre for Cancer (see p.13), which is having significant impact on our work. The continued funding which we receive from NIHR (£11m in 2009/10) is vital to our pursuit of excellence in research, and in the translation of that research to patient benefit.

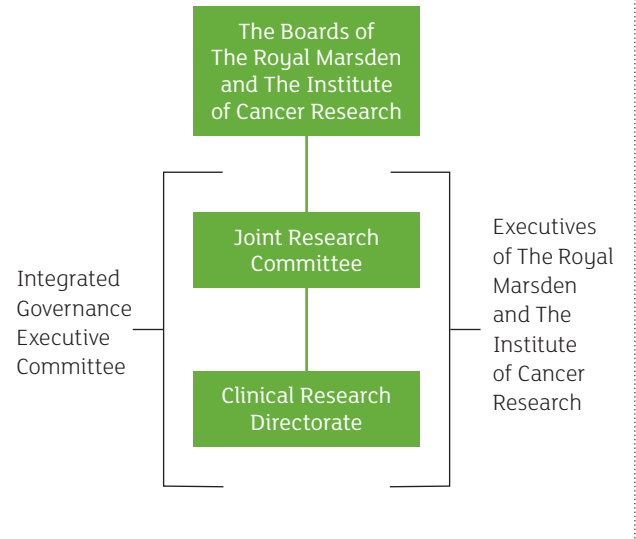
Other developments this year include the installation of a 3T-MRI scanner within the Cancer Research UK/ EPSRC Cancer Imaging Centre, which will significantly enhance the quality of our cancer imaging records.

We have continued to develop novel techniques for the delivery of radiotherapy to enhance efficacy and minimise normal tissue reactions. With our new academic partnership with the Mount Vernon Cancer Centre, we will be the only two NHS centres in the UK to use the Cyberknife robotic radiotherapy technique for treatment and research.

### Patient Involvement in Research

Being part of a clinical trial is increasingly becoming part of a patient's cancer care. Benefits to patients involved in clinical trials are notable in several ways. For example, being referred to the Drug Development Unit at The Royal Marsden and joining a clinical trial may open alternative treatment options when conventional options are limited.

### Research Governance Structure



It is important for The Royal Marsden to demonstrate user involvement in research. Users are generally defined as those people who might benefit from the outcomes of research, such as patients, family members or carers, and in some circumstances the public. A twelve-month pilot will begin shortly with a patient and carer research review panel for clinical research performed at The Royal Marsden. The panel will perform monthly reviews and advise on research documents including protocols, proposals and patient information. This contribution will compliment the work of the Research Ethics Committee and the Committee for Clinical Research by providing an integral patient and carer perspective on research.

### Financial Facts and Figures

The principal sources of income and the expenditure of our joint institution are summarised in the Financial Summary illustrations on p.60. Full and detailed statements of the financial accounts of the ICR (for the year ended 31 July 2009), The Royal Marsden NHS Foundation Trust (for the year ended 31 March 2010) and The Royal Marsden Charities (for the year ended 31 March 2010) are separately recorded in our respective Annual Reports and Accounts.

Overall, the combined annual turnover of our organisation was £325.7 million, with 93% of this total being devoted to research activities and patient care services.

The ICR is particularly indebted to its major funding partners: Cancer Research UK, Breakthrough Breast Cancer, Leukaemia & Lymphoma Research, the Wellcome Trust, the Research Councils and the Department of Health, and to many other medical research sponsors.

Commercial partners collaborating with the ICR and supporting clinical trials at The Royal Marsden during 2009 included Novartis, Pfizer, GlaxoSmithKline, Sareum, Bayer, Cougar, Elekta, MerckSerono, Synarc, Antisoma and AstraZeneca.

Many organisations also contribute support by providing funds for studentships at the ICR and clinical fellowships at the hospital. The Royal Marsden and the ICR are grateful to all the numerous organisations and supporters who have made investments in our research activities.

### Fundraising

The ICR and The Royal Marsden wish to express their profound gratitude to all of their supporters who come together in the fight against cancer and in helping us towards our ultimate goal: that people may live free from the fear of cancer as a life threatening disease.

Supporters of The Royal Marsden Cancer Charity have raised over £16 million this year. Their generosity means that we can provide the best facilities for patients and introduce the latest technology and offer the highest standard of care.

During the year, The Royal Marsden Cancer Charity made possible the redevelopment of the hospital's Haemato-Oncology Unit in Sutton, significantly improving the standard of outpatient and day care environments. The opening of the Wolfson Surgical Suite doubled surgical capacity and the new Critical Care Unit in Chelsea is Europe's largest critical care facility for cancer patients. This will further improve our excellent survival rates for the most complex cases and will house one of the most sophisticated clinical information systems currently available in only a handful of the most advanced intensive care units in the UK. The Charity makes a vital contribution to treatment and research with recent investment of £16 million in a major Centre for Children and Young People with cancer, which will open in 2011. The Centre will include facilities for drug development, where new anti-cancer agents for children and young adults can be tested on site for the first time anywhere in the world. The Charity is also funding installation of Cyberknife to extend our research programme into the latest and best radiotherapy treatments.

Throughout the year the ICR has been fortunate enough to be supported by many loyal fundraisers. Intrepid sailor Mary Falk has continued to take part in gruelling races in support of the ICR and Graeme Chapman's annual 'Climb of Life' walk has grown from strength to strength. Our ever-growing portfolio of events and the innovative fundraising activities conducted by our supporters continues to yield much needed income. We would especially like to thank The Freemasons' Grand Charity for their continued support of our prostate cancer research. Other generous long term supporters of our research programme include the PF Charitable Trust, the Lewis Family Charitable Trust, Rosetrees Trust, the Head and Neck Cancer Research Trust, the Peacock Charitable Trust and the Isle of Man Anti-Cancer Association.

The ICR's Everyman Male Cancer Campaign has enjoyed the substantial support of many corporate partners including Screwfix, Topman, The Football Association and The Professional Footballers' Association: our fundraiser, Tacheback, was also very successful once again.

The Royal Marsden and the ICR wish to record their gratitude to all those who remembered us in their wills, all law firms taking part in the ICR's 'Will for Free' scheme, and to the many individuals who have supported our work through giving donations, organising events or attending fundraising occasions.

### Professor Peter Rigby FRS

Professor Peter Rigby FRS indicated earlier this year his wish to retire from his post as Chief Executive of the ICR in light of his appointment as Deputy Chairman of the Wellcome Trust. The ICR advanced under his 11 year leadership to become one of the outstanding academic research institutions in the world. This could not have been achieved without his drive, judgement and dedication to detail. Professor Rigby has been elected to the Fellowship of the Royal Society, further confirmation of his distinction within the scientific community.

Professor Rigby will be succeeded by Professor Alan Ashworth FRS. He has been Professor of Molecular Biology at the ICR for 13 years, and Director of our Breakthrough Toby Robins Breast Cancer Research Centre for 11 years. Professor Ashworth commands wide respect not just in this country but all over the world for his scientific successes and management skills. He will take up his new post in January 2011.

### Mrs Tessa Green CBE

Tessa Green is stepping down as Chairman of The Royal Marsden at the end of October 2010 after a 16 year association with the Hospital as Chairman of the Research Ethics Committee, and subsequently as Chairman of The Royal Marsden NHS Foundation Trust. Under Tessa's leadership, The Royal Marsden became one of the country's first Foundation Trusts in 2004, and it has expanded its operation significantly, developing a service partnership with Kingston Hospital, and a research partnership with the Mount Vernon Cancer Centre. Tessa has also ensured through the Trust and The Royal Marsden Cancer Charity that extensive modernisation has taken place on the Chelsea and Sutton sites, to create the best environment for 21st century medicine and science. Her successor is due to be appointed in October 2010.

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**Professor Alan Ashworth FRS FMedSci**

Professor of Molecular Biology, Co-Director of Research Integration, The Royal Marsden and The Institute of Cancer Research.

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**Professor David Cunningham MD FRCP**

Professor of Cancer Medicine, Co-Director of Research Integration, The Royal Marsden and The Institute of Cancer Research.



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## Delivering Results to Guide Patient Care – An Introduction by Our Co-Directors of Research Integration

*“The integration of The Royal Marsden NHS Foundation Trust clinical units and The Institute of Cancer Research scientists will enhance the progress of drug discovery to clinical implementation.”*

— Professor David Cunningham

## Delivering Results to Guide Patient Care – An Introduction by our Co-Directors of Research Integration

Professor David Cunningham MD FRCP and Professor Alan Ashworth FRS FMedSci

The Royal Marsden NHS Foundation Trust (The Royal Marsden) and The Institute of Cancer Research (ICR) form the largest comprehensive cancer centre in Europe. Together, we work in close partnership, which enables scientific research to be translated efficiently into effective clinical practice, with the ultimate aim of developing better treatments for the benefit of cancer patients worldwide. We often characterise our approach to cancer research as ‘bench to bedside’, meaning that there should be a constant, two-way interaction between laboratory scientists and clinicians. We have the unique opportunity of achieving this interaction as one integrated organisation – this integration is also key to tailoring treatment to the individual patient’s disease. To ensure we achieve the maximum benefit from this partnership, Professors David Cunningham and Alan Ashworth have been appointed as Co-Directors of Research Integration. Their role is to ensure science and clinical practice act synergistically to benefit patients across the entire spectrum of The Royal Marsden’s and the ICR’s activities.

### A Personalised Approach to Cancer Therapy

It has long been recognised that cancer patients are different, and that every type of human cancer is comprised of subgroups which respond to treatment in different ways. A personalised approach to cancer therapy is now possible for a number of tumour types, which enables more effective and less toxic treatment for patients who have specific genetic mutations. However, improvements in our understanding of cancer biology, our ability to identify novel therapeutic targets specific to individual tumour sites, and the way in which we evaluate new drugs within clinical trials, are all required in order to deliver the most effective treatment to cancer patients as quickly as possible. There is also an urgent need to identify clinically useful tissue biomarkers that accurately predict response to treatment, so that particular cancer therapies can be selected for individual patients.

### The Centre for Molecular Pathology

A new state of the art Centre for Molecular Pathology is being built within the grounds of The Royal Marsden in Sutton, and will be complete in 2012 (see Figure 1).

The Centre is pivotal in our mission of translating insights from leading-edge laboratory studies to long-term patient benefit, and will house the scientific activity required to achieve this. The Centre aims to establish and develop: new and reliable molecular diagnostics and biomarkers to enable the personalisation of cancer treatments; measurements that indicate disease state; a driving force for the clinical development of novel anti-cancer drugs; and to identify new molecular targets in a range of tumour types using advanced molecular profiling technologies. Once built, the Centre will house the expanded Molecular Diagnostics Laboratory, which is currently situated in the Section of Haemato-oncology within the ICR.

**Figure 1**

Artist’s Impression of The Centre for Molecular Pathology



### Interrogation of the Cancer Genome

By integrating new DNA sequencing technologies, such as next generation sequencing, with pre-existing established molecular techniques, we will be able to discover novel therapies for future patients. RNA interference screens are increasingly used in the laboratory with the aim of identifying key genes that control disease progression by selectively silencing gene expression, and are a powerful tool used to enhance various steps of the drug discovery process. The information obtained by combining these results with molecular profiling techniques has already led to the identification of drugs that specifically inhibit novel therapeutic targets.

### Use of Tissue to Identify Novel Biomarkers and Therapeutic Targets

Collecting sample tissue is central to our goal of making new discoveries that have a direct impact on improving personalised care, and is a way in which patients allow us to push international boundaries for research. Patients are asked to consider giving general written consent for

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*“The latest technological advances will be utilised to interrogate different genetic properties of tumours on a genome-wide scale.”*

the future use of their tissue when they are first seen at The Royal Marsden for these very reasons. Plans are being made for the implementation of a formal tissue bank, so that samples can be stored for future research. This will provide the large number of processed samples, tissue sections and microarrays essential to identify genes which are consistently up or down regulated in specific tumour types. Prospective tissue collection and the inclusion of translational sub-studies within multi-centre randomised controlled trials will be necessary to validate and qualify predictive biomarkers of response, before they are utilised in clinical practice.

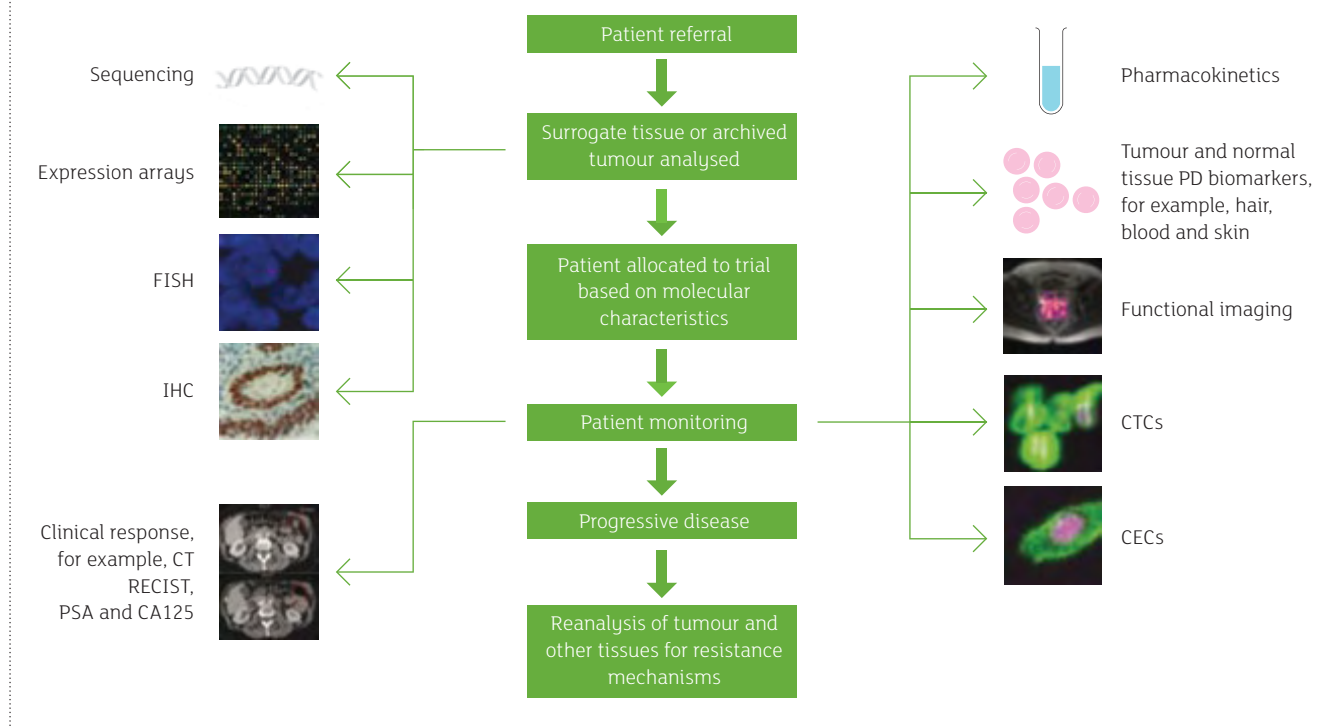
**Figure 2**

**Future Clinical Track for Early Phase Clinical Trials**

We are including the following measures in our early phase studies to further our knowledge of cancer biology and to improve the evaluation of novel therapies. This will hopefully lead to the delivery of effective personalised treatment according to the molecular characteristics of the tumour and the patient, improving the outcome for patients with cancer.

*With kind permission from Dr Johann de Bono*

- FISH fluorescent in-situ hybridisation
- IHC immunohistochemistry
- PD pharmacodynamic
- CTCs circulating tumour cells
- CECs circulating endothelial cells
- CT RECIST computed tomography response evaluation criteria in solid tumours
- PSA prostate specific antigen
- CA125 a protein found in ovarian cancer cells



**Early Anti-cancer Drug Development**

The success of modern Phase I trials is dependent on results from detailed preclinical studies that improve our understanding of target biology and drug pharmacology. To ensure we achieve this success, numerous strategies will be incorporated into our clinical studies (see Figure 2). *A priori* hypotheses (which are prospective rather than retrospective analyses) relating to expected molecular and biological effects will be incorporated into early trial designs to improve accuracy and increase statistical power compared with conventional statistical analyses. There will be integration of analytically validated and clinically qualified biomarkers at the earliest stages of drug development, which will allow for a more robust measurement of drug safety and efficacy. Molecular proof-of-concept investigations will be undertaken at an early stage, before drugs are selected for evaluation within larger clinical studies. Stratification biomarkers will be used to enrich Phase III clinical trials by increasing the responder population, reducing the size, time and cost, and improving the overall results of clinical studies for long-term patient benefit. Molecular markers will be correlated with response and survival data, and evaluation of tissue from patients who do not respond to treatment will lead to the detection of mechanisms of resistance to targeted therapy.

**Clinical Pathology Accreditation**

The Molecular Diagnostics Laboratory is licensed for both Good Clinical Laboratory Practice (GCLP) and Clinical Pathology Accreditation (CPA). The former permits the analysis of tissue samples for retrospective biomarker studies, and the latter ensures accuracy, reliability and timeliness of delivering molecular marker results if they are required for diagnostic purposes, or if the patient's treatment will be directly affected by the results. Having CPA also allows the evaluation and validation of predictive biomarkers within the context of prospective trials.

**Future Directions**

Ultimately, we hope to deliver cancer care in which the treatments are dove-tailed to the molecular characteristics of both the tumour and the patient, thereby increasing clinical effectiveness and outcome for patients with cancer.

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Professor Stephen Johnston PhD FRCP

Director of the National Institute for Health  
Research Specialist Biomedical Research  
Centre for Cancer, The Royal Marsden  
and The Institute of Cancer Research.



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## The Specialist Biomedical Research Centre for Cancer – Delivering Personalised Cancer Treatment in the Clinic

*“Cancer treatment is undergoing a revolution – previous one-size-fits-all approaches to therapy are being replaced by tailored personalised treatment strategies that match the molecular defects in each cancer to appropriate targeted therapies.”*

— Professor Stephen Johnston

## The Specialist Biomedical Research Centre for Cancer — Delivering Personalised Cancer Treatment in the Clinic

Professor Stephen Johnston PhD FRCP

There are 10 themes within the National Institute for Health Research (NIHR) Specialist Biomedical Research Centre (BRC) for Cancer at The Royal Marsden NHS Foundation Trust (The Royal Marsden) and The Institute of Cancer Research (ICR), which all facilitate translation of knowledge about the basic science of cancer into clinical practice. Our latest developments have focused around an improved understanding of the molecular development of cancer, which in turn will deliver better outcomes for patients with cancer via personalised treatment strategies.

The strategy of our Specialist BRC for Cancer is to rapidly move the science of cancer from ‘bench to bedside’ in an integrated manner, and this is exemplified by the development of personalised cancer treatments. The discovery of potential candidate genes for targeted therapy drives the development of new anti-cancer drugs in the Section of Cancer Therapeutics and Clinical Pharmacology Unit, which can then be rapidly tested in Phase I clinical trials. Promising drugs are then taken into Phase II/III trials in various clinical units within The Royal Marsden and, if successful, may finally be implemented into routine clinical practice.

We now have several examples of this ‘personalised treatment’ strategy in practice, which illustrate our increasing ability to bring research findings from the laboratory bench rapidly to the clinical bedside.

### PARP Inhibitors

In June 2009, scientists at The Royal Marsden and the ICR, in collaboration with KuDOS Pharmaceuticals, published pioneering results from a Phase I clinical trial of the poly(ADP-ribose) polymerase (PARP) inhibitor drug, olaparib in the prestigious *New England Journal of Medicine*. This work has been cited as a classic example of ‘bench to bedside’ translational research that has yielded a personalised treatment with a completely new class of anti-cancer treatment.

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*“We now have several examples of this ‘personalised treatment’ strategy in practice, which illustrate our increasing ability to bring research findings from the laboratory bench rapidly to the clinical bedside.”*

**Figure 1**

Through the Specialist BRC for Cancer basic science can be rapidly translated to clinical practice.



Scientists at the ICR originally discovered the *BRCA2* gene 15 years ago, and found an increased risk of developing cancer due to mutations of the *BRCA2* gene impairing the cancer cell’s ability to repair DNA. They subsequently established that these cancers were especially sensitive to a new class of drugs called PARP inhibitors, which target the cancer cells but leave healthy cells relatively intact. This led to the first clinical trial in the world to test this concept in patients with inherited forms of advanced breast, ovarian and prostate cancer due to *BRCA1/2* mutations.

The results of this early clinical trial exceeded expectations, and despite having previously received many standard therapies, the treatment was effective in more than half of the patients. Indeed, one of the first patients to be given the treatment is still in remission after two years. Patients experienced very few side effects, and some reported that the treatment was significantly easier than chemotherapy.

This is one of the first successful examples of a new type of ‘personalised treatment’ in which the treatment works by targeting a specific molecular defect within the cancer, and where a molecular diagnostic test can identify those patients for whom this would be the most effective treatment. Professors Stan Kaye and Alan Ashworth further elaborate on their progress with PARP inhibitors on page 19.

### Molecular Diagnostics

The cornerstone of most research programmes within our Specialist BRC for Cancer has been the development of molecular biomarkers that can help diagnose cancer, work out the prognosis of different sub-types of the same cancer, or can predict which cancers will respond to different therapies or pinpoint those that will ultimately develop resistance to them.

### Research Highlights of the Specialist Biomedical Research Centre

1. In breast cancer, we have developed a new immuno-histochemically based prognostic score (IHC4) based on antibody analysis of tissue sections (immunohistochemistry) which will cost less than £100, and provides at least as much information on outcome in hormone receptor positive (ER+) early stage breast cancer as a test (OncotypeDx) that costs over £2,500. This is now being validated in a prospective clinical trial. The IHC4 has the prospect of being implemented in pathology laboratories around the country with enormous cost savings not only from testing, but also possibly from avoiding adjuvant chemotherapy that may not be required by patients stratified as very low risk.
2. In terms of new treatments for different breast cancer sub-types, in patients with metastatic breast cancer that tests positive for both Estrogen Receptor (ER) and Human Epidermal growth factor Receptor 2 (HER2), we led an international trial that showed that a combination of letrozole and lapatinib significantly enhanced progression free survival and clinical benefit rates compared with letrozole and placebo, leading to a new licensed indication. We are also conducting a Phase II trial of a novel inhibitor of the FGFR protein in women with advanced breast cancer who have amplified copies of the *FGFR* gene.
3. In prostate cancer, we are utilising tissue samples collected from patients enrolled in a series of National Radiotherapy trials of dose and fractionation. Tissue biomarkers of cell death (apoptosis) may be a significant determinant of clinical outcome independent of grade, stage and prostate-specific antigen (PSA) level – a chemical produced by the prostate, which is usually raised in prostate cancer. Our research also indicates that tumours that express a protein called B-cell lymphoma 2 (Bcl-2) could be used to individualise radiotherapy dose, and we have also identified further key genetic variants that predict for development of prostate cancer.
4. In paediatric oncology, we have shown that amplification of the *MYCN* gene occurs frequently in high risk neuroblastoma, rhabdomyosarcoma and medulloblastoma – cancers that arise in developing sympathetic nervous tissue, connective tissue and the brain, respectively. Stratification of treatment for children with these tumours now occurs according to *MYCN* gene amplification. Meanwhile, integrated molecular profiling of paediatric high grade glioma, an aggressive brain tumour, has revealed the frequency of aberrations of IGF-1R and PDGFR pathways, providing a new focus for early Phase I drug development studies in children with these tumours who have a very poor prognosis.

5. In gastro-intestinal cancer, we have shown that colorectal cancer cells deficient in the *MSH2* gene are extremely sensitive to the anti-folate drug methotrexate. This has led to a new clinical trial being initiated for patients with advanced cancer that contains this molecular defect. In oesophagogastric cancer, we are continuing to assess molecular determinants of response to chemotherapy utilising a unique set of clinical samples.
6. In evaluating novel targeted therapies, our studies have demonstrated proof-of-principle for a novel class of anti-cancer drug that targets the PI3K/AKT pathway, which regulates a diverse range of cellular functions. We have utilised assays that show AKT phosphorylation being inhibited in both normal and tumour tissue during our evaluation of a first-in-class AKT inhibitor. These assays are aimed at enhancing development of these novel anti-cancer therapies, thus ensuring that the most appropriate cancers are targeted in order to gain maximum benefit.

### The Centre for Molecular Pathology

As outlined above, delivery of modern cancer treatment now revolves around accurate diagnosis and molecular sub-typing of cancer, determining which key oncogenic pathways are active in an individual patient's tumour. As new therapies are developed against these molecular targets, for the first time, we are starting to arrange an individual patient's treatment plan based around their own type of cancer. This will yield better results compared to conventional treatment, and will be a cost-effective way of ensuring that these novel therapies are used only in those patients who are likely to derive benefit.

The BRC's new Centre for Molecular Pathology, funded by the NIHR, together with support from the Wolfson Foundation, will substantially enhance our capacity to deliver personalised treatment through: systematic profiling of patients' tumours; the development of molecular diagnostics for routine clinical use; and the discovery of novel targets for the next generation of cancer drugs. Planning permission has now been granted for the three-storey Centre, which will house up to 100 scientists and clinical research staff.

## Basic Science

We carry out basic laboratory research in the areas of cancer gene discovery, cell and molecular biology and targeted cancer therapeutics discovery.

2009/10 basic research highlights at The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research include work by Professors Stan Kaye and Alan Ashworth on PARP inhibitors and their promising results in the treatment of ovarian cancer. Professor Nazneen Rahman overviews her research on identifying breast cancer genes, and how this leads to improving patient outcome by finding new treatment strategies to prevent breast cancer. Professor Richard Marais and colleagues describe how improved knowledge of the BRAF protein is leading to advances in melanoma treatment.

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### New Treatments for Melanoma

Professor Caroline Springer  
Professor Richard Marais  
Dr James Larkin

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### Finding Breast Cancer Genes

Professor Nazneen Rahman



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PARP Inhibitors –  
Targeting Cancer Weakness  
Shows Promise in Ovarian Cancer  
Professor Stan Kaye  
Professor Alan Ashworth



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**Professor Stan Kaye MD FRCP FRCR FRSE FMedSci**  
Cancer Research UK Professor of  
Medical Oncology, Head of the Drug  
Development Unit, The Royal Marsden  
and The Institute of Cancer Research.

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**Professor Alan Ashworth FRS FMedSci**  
Professor of Molecular Biology,  
Director of the Breakthrough Toby  
Robins Breast Cancer Research Centre,  
The Institute of Cancer Research.



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## PARP Inhibitors – Targeting Cancer Weakness Shows Promise in Ovarian Cancer

*“The clinical results with PARP inhibitors in ovarian cancer represent one of the most exciting developments in its treatment in the past decade. They represent the best example yet of a real opportunity to introduce personalised therapy, in order to help a large population of women with this disease.”*

— Professor Stan Kaye

## PARP Inhibitors – Targeting Cancer Weakness Shows Promise in Ovarian Cancer

Professor Stan Kaye MD FRCP FRCR FRSE FMedSci and Professor Alan Ashworth FRS FMedSci

Five years ago, Professor Alan Ashworth's group at the ICR, in collaboration with colleagues from KuDOS Pharmaceuticals, showed that cancer cells with *BRCA* gene mutations are particularly sensitive to treatment with poly(ADP-ribose) polymerase (PARP) inhibitors. This is one of the best examples of the phenomenon called synthetic lethality, whereby a treatment may work with a patient's specific cancer-associated molecular fault to create a combination of defects that are lethal to cancer cells. PARP inhibitors block the action of the PARP enzyme, which repairs DNA damage. In healthy cells, as well as some cancer cells, blocking PARP has little consequence, as its function in DNA repair is carried out by the *BRCA1/2* proteins. However, in cancer cells that have *BRCA* mutations, blocking PARP leaves the cells unable to repair damage to their DNA, which in turn causes the cancer cells to die. This is because cells with *BRCA* mutations have a defect in a specific DNA repair pathway called homologous recombination. PARP inhibitors attack this Achilles' heel, resulting in a potentially highly selective personalised therapy.

### First Clinical Trials of PARP Inhibitors in *BRCA*-associated Cancer Patients

As a result of these laboratory-based studies, which demonstrated remarkable and promising potential for PARP inhibitors, we approached the treatment of the first patient with *BRCA*-associated ovarian cancer with cautious optimism. The drug we tested, in collaboration with KuDOS Pharmaceuticals (later taken over by AstraZeneca), was called olaparib.

It soon became apparent that not only was olaparib well-tolerated, with patients typically remarking "this is nothing like chemotherapy", but we were also able to show definite evidence of tumour shrinkage in several patients, both on Computed Tomography (CT) scans and by falling levels of the tumour marker, cancer antigen 125 (CA125). In the first-ever Phase I trial of an oral PARP inhibitor in patients with *BRCA* mutations, conducted at the ICR and the Netherlands Cancer Institute, we established that 200 mg twice daily was an appropriate dose for use in further trials, and reported the first evidence of efficacy.

We went on to treat a total of 50 patients with *BRCA*-associated ovarian cancer, all of whom had progressive disease growth following previous extensive chemotherapy. A clinical benefit was seen in 46% of the cases and the median response to olaparib treatment lasted seven months. Interestingly, we found a greater likelihood of response to olaparib when there had been a longer interval between previous platinum-based chemotherapy and disease progression. Treatment was well-tolerated, with a minor degree of nausea being the main side effect. These promising results were virtually duplicated in two international multicentre trials in June 2009, which confirmed the level of activity and tolerance in both *BRCA*-related ovarian and breast cancer.

The next step in moving toward registration and approval of this treatment for this well-defined group of patients is the provision of evidence from randomised trials. This will inevitably mean a delay before the treatment becomes more widely available for *BRCA*-associated cancer. However, several companies have now realised the potential for PARP inhibitor therapy in cancer, and the competition that this provides should help to speed up the process.

It is important to recognise that PARP inhibitor therapy is not intended to replace chemotherapy, rather it can provide an alternative treatment at an appropriate time. Indeed, we have been interested in establishing the potential of subsequent chemotherapy for patients whose disease has progressed on olaparib treatment, since there are theoretical reasons for thinking that this will not be effective. In our first report on this topic we noted that 12 of 27 (45%) patients previously treated with olaparib did in fact respond to paclitaxel and/or carboplatin chemotherapy. Although these initial response data are intriguing, further data, particularly on response duration, are needed before firm conclusions can be drawn.

### Broader Applications for PARP Inhibitors

It is recognised that *BRCA* mutation-related ovarian cancer that is associated with a family history of cancer is relatively rare, accounting for 11–15% of unselected cases. Other cancers can be associated with *BRCA* mutations (indeed we have seen a long-lasting response in a patient with *BRCA*-associated prostate cancer treated with olaparib), but these are also rare.

However, it is now apparent that a significant proportion of patients with sporadic ovarian cancer (no family history), particularly those with the common high grade serous histopathological subtype, may have loss of normal *BRCA* function either through a mutation occurring

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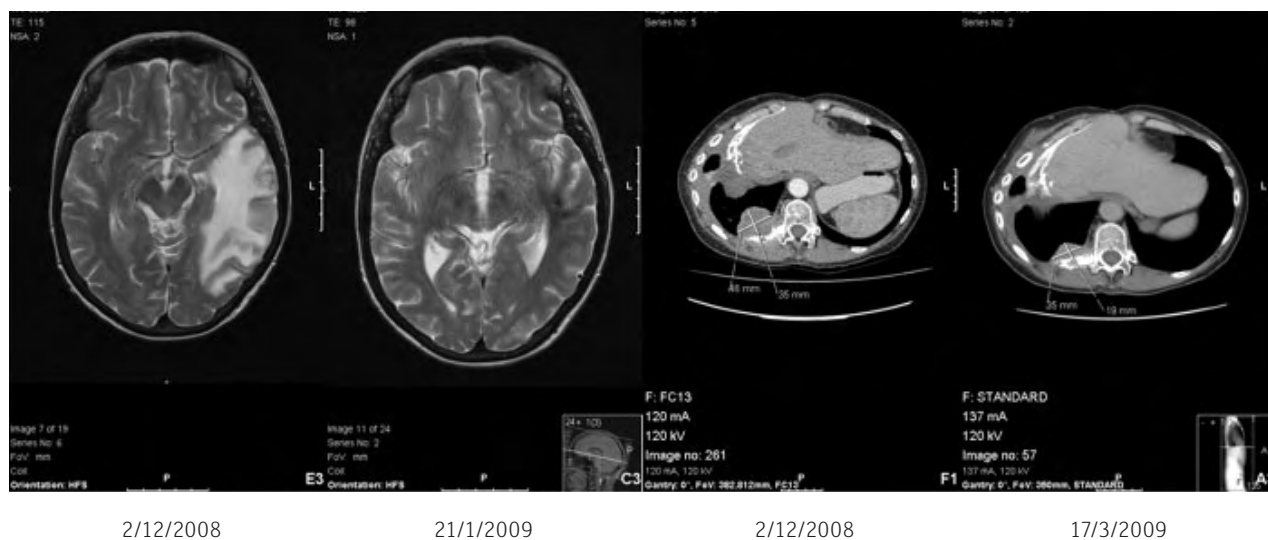
*"It is now apparent that a significant proportion of patients with sporadic ovarian cancer (no family history) should exhibit similar sensitivity to PARP inhibition, raising the exciting possibility of a much broader application for this approach."*

in their tumour as it develops (somatic mutation), or for other reasons. These cancers also have a homologous recombination deficiency, and therefore should exhibit similar sensitivity to PARP inhibition, raising the exciting possibility of a much broader application for this approach. Indeed, in the past year we have clearly demonstrated that ovarian cancer patients without germ line (familial) *BRCA* mutations can benefit from PARP inhibitor treatment, both with olaparib and with another oral PARP inhibitor,

**Figure 1**

Response in Brain and Pleural Cavity After Six Weeks of Treatment with Olaparib in a Patient with *BRCA* Negative Sporadic Cancer.

The scans show a dramatic response in the brain, as well as evidence of benefit in the disease in the chest after six weeks of treatment with olaparib, and no other anti-cancer treatment.



known as MK 4827 (made by Merck & Co.), which has recently completed its first-in-man Phase I trial in our Drug Development Unit. These patients, with so-called 'BRCAness', typically will have exhibited response to prior platinum-based therapy before developing progressive disease. In one such example, a 50-year-old patient had developed a brain metastasis just prior to olaparib treatment; remarkably this responded completely to six weeks of olaparib treatment alone (Figure 1). This patient had no evidence of a *BRCA* mutation (germ line or somatic), but an immunohistochemical analysis of tissue samples did show evidence of the loss of a functional *PTEN* gene. Alan Ashworth's team has shown that *PTEN* is also linked to homologous recombination deficiency and therefore this case supports our hypothesis that other causes of homologous recombination deficiency might render cancers susceptible to PARP inhibition.

Most recently, the efficacy of PARP inhibitor treatment in sporadic ovarian cancer was confirmed in a key study from Canada. A total of 55 patients with high grade serous disease were treated with 400 mg of olaparib twice daily; the level and duration of response was in keeping with that seen in our first trial.

### Combining Treatments

The field of PARP inhibitor therapy is evolving rapidly, and now includes the assessment of combination treatment. Preclinical evidence supports the use of PARP inhibitors together with chemotherapy, and various schedules are being tested (including three examples in our Drug Development Unit). Generally the doses of both PARP inhibitor and cytotoxic agents need to be modified, and further information from our laboratory studies will be very important in guiding these combinations in the appropriate direction.

### The Future of PARP Inhibitors

Tumour synthetic lethality using PARP inhibitors is an excellent example of personalised medicine. This is a method of guiding patient selection by analysing various molecular genomic characteristics (so-called predictive biomarkers) and can provide the best value-for-money for expensive new agents. In this context, the development of laboratory-based assays for homologous recombination deficiency is a high priority for our group. Over the next few years, it is anticipated that this new approach to treatment will change the management not only of patients with *BRCA*-associated cancer, but also of a broader population of patients with sporadic ovarian and other cancers.

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Professor Nazneen Rahman PhD FRCP FMedSci  
Professor of Human Genetics,  
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The Institute of Cancer Research.



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## Finding Breast Cancer Genes

*“Identifying genes that can cause breast cancer is essential to increasing our understanding of the disease, to identifying people at increased risk of the disease and ultimately in finding strategies to prevent breast cancer.”*

— Professor Nazneen Rahman

## Finding Breast Cancer Genes

Professor Nazneen Rahman PhD FRCP FMedSci

Over the last two decades there has been an explosion of knowledge about why breast cancer sometimes affects multiple family members. The Royal Marsden NHS Foundation Trust (The Royal Marsden) and The Institute of Cancer Research (ICR) have been fundamentally involved in many of these discoveries and their translation into the clinic. The advent of new technologies that allow fast, cheap and accurate DNA analysis on a scale unimaginable only a few years ago, now heralds a new era of both gene discovery and utilisation in clinical practice.

### Familial Breast Cancer

There are thousands of families affected by familial breast cancer in the UK, and we see hundreds of families in the Clinical Cancer Genetics Unit at The Royal Marsden each year. Breast cancer is a common condition; about 1 in 10 women will develop the disease. Because breast cancer is common, it is not unusual to see more than one affected individual in a family. Sometimes, however, there are many cases of the disease in a family, suggesting that genetic factors are acting to increase the risk of breast cancer.

### Genetic Predisposition to Breast Cancer

Fifteen years ago, scientists at the ICR identified the *BRCA2* cancer gene. *BRCA2* and another cancer gene called *BRCA1*, are high risk cancer predisposition genes. This means that faults (mutations) in the gene are associated with high risks of breast cancer – more than 10 times the risk in the general population – resulting in a risk of breast cancer of 60–90% over a lifetime for a *BRCA* mutation carrier (see Figure 1). We now know that *BRCA1* and *BRCA2* are involved in repairing damaged DNA, and we have been able to show that mutations in four other DNA repair genes – *ATM*, *CHEK2*, *BRIP1* and *PALB2* – also increase an individual's risk of developing breast cancer. These genes are associated with somewhat smaller cancer risks, around 2–3 times higher than the general population risk.

Mutations in genes like *BRCA2* are very rare, and are only present in about 1 in 1000 individuals in the UK. However, our genomes also contain many common genetic variants, known as polymorphisms. Most common variants are innocuous, but some can be associated with small increases in risk of disease. In collaboration with colleagues in Cambridge, we have, in the last year, performed the largest breast cancer study to look for common variants associated with the disease. We looked at 582,886 common polymorphisms in 3,659 women with familial breast cancer, and in 4,897 control individuals without cancer. We then looked at the polymorphisms that showed the most promising associations with breast cancer, from this first stage, in a further 12,576 women with breast cancer and 12,223 control individuals. This

allowed us to identify five new common variants that increase an individual's risk of breast cancer, bringing the total number of common variants associated with breast cancer to 18. Interestingly, the majority of the common variants are associated primarily with oestrogen-positive breast cancers (breast cancer cells that contain oestrogen receptors), whereas *BRCA1* is strongly associated with oestrogen-negative cancers. These common variants only very slightly increase the risk of breast cancer and together only account for about 8% of the familial risk of breast cancer (see Figure 1). However, our study clearly indicates that there are many other promising common variants that require evaluation. The necessary follow-up studies are now being undertaken by a large international consortium that includes samples from over 20,000 women with breast cancer and 20,000 controls. We are optimistic that this will lead to the discovery of several more common variants associated with breast cancer within the next few years.

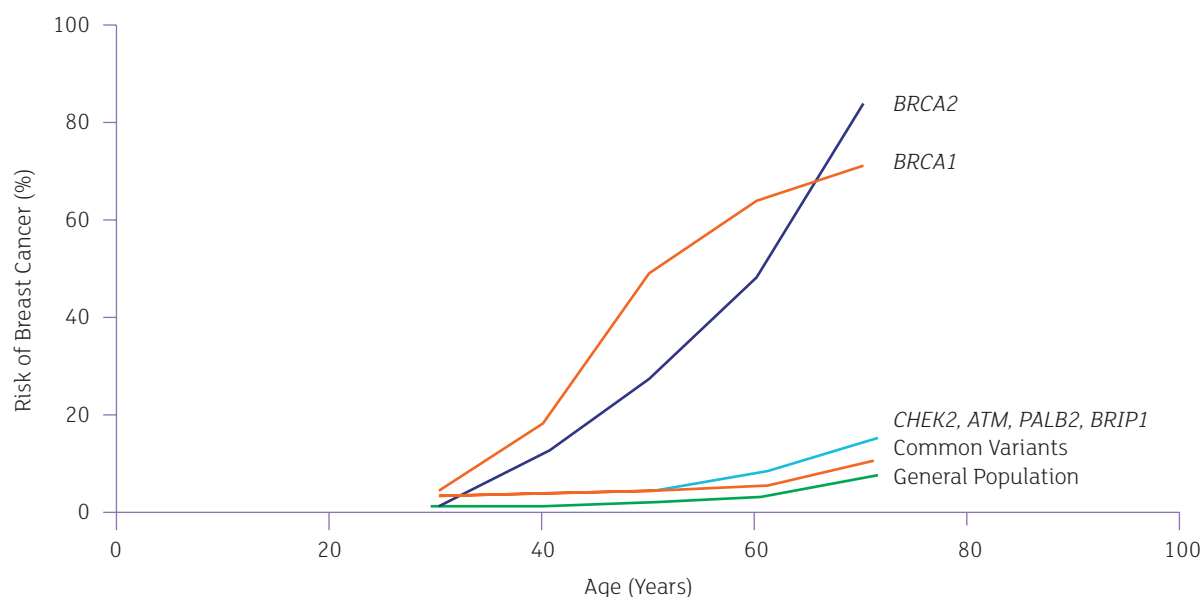
### Clinical Impact of Breast Cancer Genes

What impact does knowledge of breast cancer genes have for patients? For families with a strong history of breast (and ovarian) cancer we are able to undertake gene testing to see if a *BRCA1* or *BRCA2* mutation is responsible. Our Clinical Genetics Unit at The Royal Marsden has pioneered the management of women with *BRCA* mutations in the carrier clinics set up by Professor Ros Eeles. Over the last year, our joint Royal Marsden-ICR clinical academic unit has developed new protocols for the management of women with familial breast cancer that is not due to *BRCA* genes, to ensure that such families can be consistently allocated extra mammographic surveillance on the basis of risk of breast cancer. These protocols have been implemented and audited, and are now in general use throughout the region.

### Finding New Breast Cancer Genes

Despite the huge progress that has been made in understanding genetic predisposition to breast cancer, we know that at least 70% of the genetic risk of breast cancer is currently unexplained. This means that for the majority of breast cancer families that we see in clinic, we are not able to provide an explanation for why several relatives have been affected by the disease. Therefore our primary research focus remains to identify further breast cancer genes. This will allow us to provide better, individually-tailored information and management for families. Increasingly, there is the additional prospect of genetic information being helpful in deciding the optimal treatment for individuals.

**Figure 1**  
Risk of Breast Cancer in Carriers of Predisposition Genes



### Future Prospects

Over the last few years, there has been a seismic technological shift in our ability to analyse DNA. Whereas a few years ago we were able to look at fewer than 100 genes, we are now able to look at nearly all 20,000 genes in one experiment. Although there are still challenges with respect to the cost, data handling and analysis of such experiments, they offer the opportunity for new gene discovery on an unparalleled scale. Our rich resource of breast cancer families places us in a very strong position to use new technologies, such as next-generation sequencing, to identify new breast cancer genes, and our integrated clinical genetics unit will then allow us to lead initiatives to bring testing and management protocols for new genes into the clinic.

New sequencing technologies will also revolutionise clinical utility of existing breast cancer genes. Currently, gene testing for *BRCA1* and *BRCA2* is very expensive and takes several weeks. As a result, *BRCA1* and *BRCA2* gene testing within the NHS is currently restricted to families in which there is a strong likelihood of finding a *BRCA* mutation. A considerable number of families that fall below this threshold also have mutations, and identification of mutations

has considerable clinical utility, both for individuals with cancer and their relatives. New DNA sequencing technologies will allow us to develop much cheaper and faster ways of gene testing. In turn, this will allow many more individuals access to gene testing and hopefully within the next few years we will be able to incorporate *BRCA* testing into the mainstream management of cancer patients, as part of the development of an optimised, personalised management plan.

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*“New sequencing technologies will also revolutionise clinical utility of existing breast cancer genes.”*

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**Professor Caroline Springer**

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## New Treatments for Melanoma

*“Our improved knowledge of melanoma biology has facilitated the discovery of effective BRAF inhibitors. By targeting BRAF mutations in melanoma patients, we can now provide novel personalised treatments.”*

— Professor Richard Marais

## New Treatments for Melanoma

Professor Richard Marais PhD FMedSci, Professor Caroline Springer PhD FSB CChem FRSC, Dr James Larkin PhD MRCP

Skin cancers are prevalent in the UK, with over 100,000 people diagnosed with these conditions each year. There are several different types but the most common are basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). Fortunately, BCC and SCC are relatively benign diseases that can usually be cured by surgery, so although they account for over 90,000 cases of skin cancer each year, they cause only about 500 deaths. In contrast, melanoma is potentially a dangerous and lethal disease and although there are only about 10,000 cases of melanoma each year, it leads to over 2,000 deaths. The incidence of melanoma is currently doubling each decade, with the number of people developing melanoma now four times higher than in the 1970s and, in women between the ages of 15 and 29, melanoma is the most common cancer.

There is a genetic component to melanoma, but the most important trigger and the only known environmental risk is exposure to ultraviolet light. Episodes of sunburn, particularly in early childhood, increase the lifetime risk of contracting melanoma, so the rise in melanoma incidence presumably reflects the increase in sunbathing as a pastime as well as the use of sunbeds by the British population.

The last 30 years have seen little improvement in the clinical management of melanoma. The front-line treatment is surgery, as for BCC and SCC, but unlike these diseases surgery is only effective in about 80% of melanoma patients. For the 20% of patients for whom surgery is ineffective there are few treatment options, and the disease progresses into a spreading form (malignant metastatic melanoma) that has a poor prognosis, with half of patients dying within six months and fewer than 10% of patients surviving for over five years.

### Melanoma and BRAF

We began to focus our research on melanoma around nine years ago when Professor Mike Stratton (former Professor of Cancer Genetics at the ICR and currently Director of the Wellcome Trust Sanger Institute) discovered that the gene for a protein we were working on, called BRAF, was damaged (mutated) in approximately half of all cases of melanoma. BRAF is an intriguing protein that is involved in the process of cell communication. To operate normal bodily functions, our cells (around 13 billion, billion in the human body) are in constant communication with each other. To this end, they have developed sophisticated systems to control the complexity

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*“In the last few years, we have made significant progress in our understanding of BRAF biology, leading to advances in our ability to design drugs that can inhibit mutated BRAF.”*

of this transmission of information. These systems, called “signalling pathways”, not only maintain the normal *status quo*, but also allow us to respond to adverse conditions such as bacterial or viral infections, or periods of starvation. A key function of signalling pathways is to allow repair from damage by stimulating cell growth to replace cells damaged during normal bodily functions or as a consequence of wounding. Unfortunately however, if these pathways malfunction, they can stimulate cell growth and survival in the absence of the normal signals, which can ultimately lead to the development of cancer.

Melanocytes are a specialised population of pigmented cells found in the skin. They make up only a small fraction of skin cells, but they perform several important functions. Their most visible characteristic is to determine our complexion and the colour of our hair (loss of these cells in the hair bulb leads to greying in older age). However, arguably their most important function is to mediate the tanning response that protects us from the damaging effect of ultraviolet light. Professor Marais has shown that when *BRAF* is mutated in melanocytes it drives them into uncontrolled growth and survival, causing melanoma to develop.

Our colleague Professor David Barford (Co-Chairman of the Section of Structural Biology at the ICR), used X-ray crystallography to examine the molecular structure of the BRAF protein and this has allowed us to understand how the mutations that occur in the gene activate the protein. By examining the function of BRAF, Professor

Marais was able to show that a mutation by itself was not sufficient to drive melanoma, but that the acquisition of this mutation could be the first, or “founder”, event in the process that converts a melanocyte into a full-blown metastatic malignant melanoma. Importantly, he was able to demonstrate, using model systems, that when the function of the mutant BRAF is blocked in melanoma cells, we can slow down the growth of tumours.

#### BRAF and Drug Development

Based on these studies of BRAF function, researchers at the ICR and elsewhere have designed drugs tailored to inhibit BRAF. Professor Springer has been leading a team to develop drugs that target BRAF for use in melanoma patients. These inhibitors are proving highly effective against melanoma in model systems that express mutant forms of BRAF. Excitingly, the most advanced drug of this type, PLX4032/RG7204, developed by Roche, has recently been shown to mediate excellent responses in malignant melanoma patients

whose tumours express the mutant form of BRAF. Dr Larkin and his colleague Professor Martin Gore (Medical Director, The Royal Marsden) are currently assessing PLX4032 in a clinical trial of malignant melanoma patients, as part of a world-wide trial consortium.

Although patients treated with drugs that target BRAF, such as PLX4032, initially respond to treatment well, most eventually relapse and cease to respond. Importantly, Professors Marais and Springer recently discovered an unforeseen side-effect of these drugs; when another protein, called RAS, is also mutated in tumour cells, BRAF inhibitors can actually activate further cell growth. This unexpected finding will provide insight into how to improve the effectiveness of BRAF targeted drugs in patients, to both extend the duration of responses and develop methods to overcome resistance.

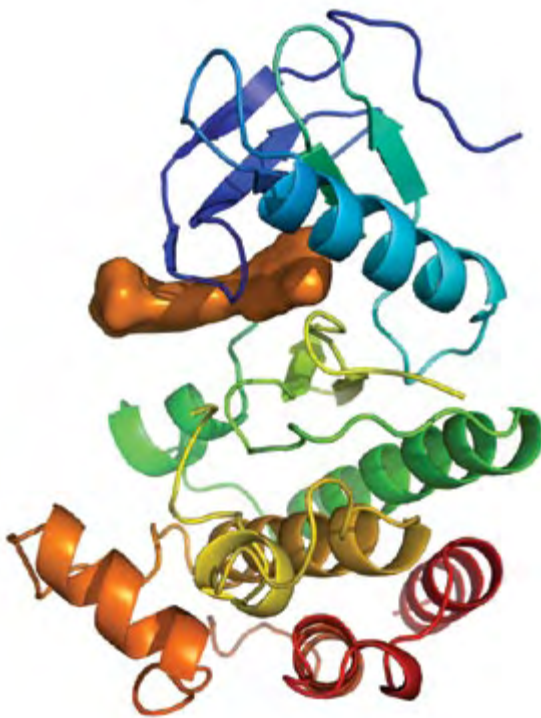
#### The Future of Melanoma and Genetics

The advances in our understanding of the role that BRAF plays in melanoma are changing the clinical management of melanoma patients whose tumours express the mutant gene. In addition, these studies are having beneficial consequences in other types of melanoma, because they have led other researchers to show that another gene, called *CKIT*, is mutated in around 5% of melanomas, and Dr Larkin and Professor Marais are currently leading a national trial to assess whether a novel drug, called Nilotinib, works in patients whose tumours express the mutant gene.

It is fair to say that the revolution in our understanding of melanoma biology that has occurred in the last decade is a paradigm shift in treatment practice. This improved knowledge is changing the clinical management of melanoma and providing real benefits for malignant melanoma patients.

**Figure 1**

A ‘ribbon diagram’ representation showing the three-dimensional structure of the BRAF protein bound to a novel inhibitor (represented by the solid orange shape in the centre of the structure).



## Translational Research

Our translational research takes discoveries in basic science forward towards early-phase clinical trials with patients. We are the only National Institute for Health Research Specialist Biomedical Research Centre dedicated to cancer in the UK, striving to translate discoveries in basic research into improved treatments for patients with cancer.

In 2009/10, our translational research highlights not only include the important work being undertaken at The Specialist Biomedical Research Centre, which was highlighted in the earlier article by Professor Stephen Johnston, but also work carried out within the fields of molecular pathology and physics. Here, Dr David Gonzalez de Castro and Professor Gordon Stamp provide an overview on the molecular pathology research carried out at The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, which is helping to contribute to the delivery of personalised care in cancer. Professor Steve Webb describes how radiation therapy can be tailored to the patient by using their individual geometry in intensity-modulated radiation therapy.

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Molecular Pathology –  
The Foundation for Personalised  
Cancer Medicine

Professor Gordon Stamp  
Dr David Gonzalez de Castro



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A Bright Future for Physical  
Techniques in Radiation Therapy

Professor Steve Webb



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**Professor Gordon Stamp** MBChB FRCPath

Professor of Cancer Pathology, The Institute of Cancer Research, and Consultant Histopathologist, The Royal Marsden.

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**Dr David Gonzalez de Castro** PhD

Head of Molecular Diagnostics, The Royal Marsden and The Institute of Cancer Research.



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## Molecular Pathology – The Foundation for Personalised Cancer Medicine

*“Molecular cancer pathology is the study of the molecular characteristics of tumour samples in order to provide a precise classification of an individual’s cancer. This is achieved by comprehensive analysis of the patient’s tumour profile (proteins, RNA and DNA) by a combination of molecular laboratory techniques.”*

— Dr David Gonzalez de Castro

The management of cancer is entering a new era following the post-genomic revolution in which there has been an explosion in the genetic knowledge of cancer. Tailor-made treatments, according to the genetic characteristics of tumours, are now becoming a reality for patients. Here at The Royal Marsden NHS Foundation Trust (The Royal Marsden) and The Institute of Cancer Research (ICR) laboratories, we are integrating research and diagnostic approaches to fully realise the potential of the structural, molecular and genetic analysis of cancer samples. This integration will enable us to deliver a 'personalised cancer diagnosis'.

### The Transformation of the Pathology Laboratory

Cancer classification and treatment is historically based on the organ of origin and microscopic structure of the cells (histopathology), and how far the disease has advanced (stage). Formerly, predicted response to particular treatments was based on these broad groupings, and patient outcome was based on statistics. However, due to the increase in our understanding of the genetics of cancer, we can now characterise each individual's cancer at a molecular level (DNA changes, RNA expression and changes in tumour-associated proteins). Owing to the variety of genetic profiles within tumours, there is a diversity found in tumour behaviour and response to anti-cancer treatments, even within the same cancer type. The availability of therapies targeting specific mutations or genetic pathways means that the treatment approach for cancer will be based on this genetic information, providing the scientific basis of personalised therapy. This type of therapy allows the selection of treatment combinations that are most likely to succeed for each patient with cancer according to their genetic profile, as illustrated in Figure 1.

### The Importance of Molecular Pathology in Cancer Medicine

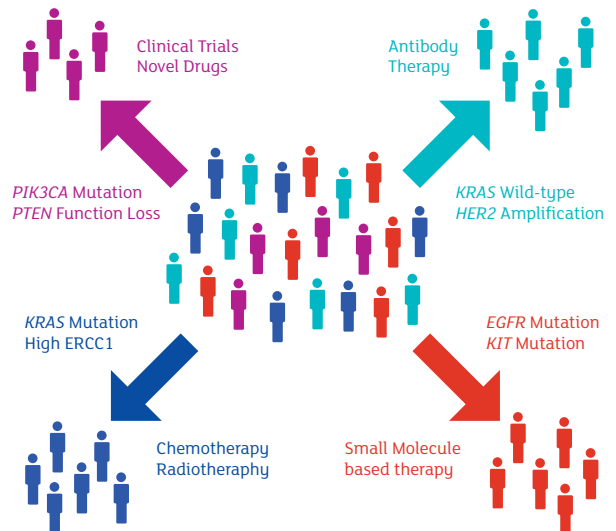
Over the last 20 years, significant achievements in cancer treatment have included the introduction of targeted antibody and small molecule-based therapies into routine clinical practice. Well-known examples include Herceptin against breast (and more recently gastric) cancers with *HER2* amplification, and Imatinib for the treatment of chronic myeloid leukaemias (*BCR-ABL* gene fusion positive).

A more recent example, which highlights the benefits of translational research in molecular pathology, is the 2010 NICE approval of the tyrosine kinase inhibitor gefitinib for the treatment of non-small cell lung cancer (NSCLC) with activating *EGFR* mutations, which constitutes 10–15% of all NSCLC in the UK. Not only are there significant improvements in progression-free survival for these patients, but the change from intravenous chemotherapy to an oral non-toxic tablet is far more acceptable to patients and is more cost-effective compared with conventional treatments. Similarly, in 2009 NICE approved the monoclonal anti-EGFR antibody

**Figure 1**

### How Molecular Pathology Integrates with Personalised Cancer Medicine

Different subgroups of tumours can now be identified, based on expression patterns of proteins, gene mutations and gene copy number alterations, amongst other abnormalities. This molecular sub-classification then has a direct impact in the management of cancer patients for which a therapeutic option is available, or alternatively, leads them to be enrolled in new clinical trials.



cetuximab for the treatment of metastatic colorectal cancer (mCRC) without *KRAS* mutations. In this case, *KRAS* is a 'negative' predictive marker and identifies the fraction of patients without *KRAS* mutations who can potentially respond to antibody treatment. We are one of the few centres in the UK that are fully accredited to provide large-scale combined histopathological diagnosis and mutation analysis of *EGFR* and *KRAS* for the management of all new patients with NSCLC and mCRC, respectively.

### Molecular Pathology at The Royal Marsden and The Institute of Cancer Research

The unique partnership between The Royal Marsden and the ICR provides a framework for the application of scientific discovery through translational research and ultimately clinical practice. A fundamental way in which we are strengthening this framework is in the development of specialised molecular pathology diagnostic laboratories to identify patients most likely to respond to targeted therapy. We employ a wide range of techniques to characterise a patient's tumour profile, including: conventional histopathology, cellular tissue microdissection, advanced high-throughput immunohistochemistry, cytogenetics, flow cytometry, fluorescence *in-situ* hybridisation (FISH) and molecular genetics. Figure 2 shows how molecular pathology techniques can identify *HER2* expression in gastric tumours.

Amongst the achievements of our multidisciplinary molecular pathology team over the last few years is the development of an integrated diagnostic report. This combines the techniques used in our molecular pathology laboratory for all new haematological malignancies diagnosed in The Royal Marsden and referring hospitals, and is part of the UK national guidelines aimed at improving patient outcome. A similar approach is likely to follow in the management of the majority of cancers in the near future. Here at The Royal Marsden and the ICR, we have implemented the largest comprehensive molecular pathology diagnostic service in the UK for soft-tissue sarcomas – a cancer type where The Royal Marsden and the ICR have internationally leading status in terms of diagnosis and treatment.

In the last year, several clinical trials at The Royal Marsden have been approved, where the analysis of molecular biomarkers will play an essential role in assessing tumour response and patient outcome for new and existing therapies. In parallel, translational research is carried out on samples from these patients at the

*“The Royal Marsden and ICR laboratories offer a unique resource of tumour samples and data, in addition to laboratory expertise. This enables us to maximise the information that can be extracted from cancer cells, whilst integrating research and clinical information, providing an excellent standard of cancer diagnosis and treatment.”*

ICR by expert teams aiming to explore the biological effect of the new drugs in the different sub-groups. The opening of the new Centre for Molecular Pathology will combine the expertise available at The Royal Marsden and the ICR in a unique multidisciplinary environment where all these advances will be consolidated, providing state-of-the-art translational research and cancer molecular diagnostics. One of the other major tasks for the Centre's laboratories will be the establishment of annotated cancer tissue and information from The Royal Marsden patients – the ‘William Marsden Cancer Bank’. This bank of data will provide a rich resource for future basic scientific and clinical cancer research.

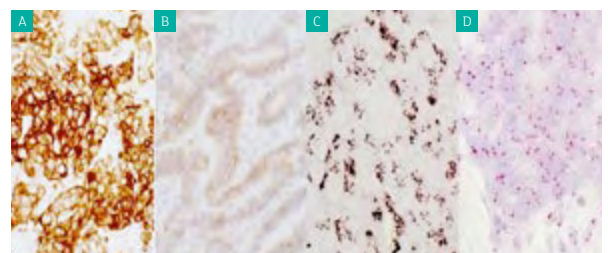
### What the Future Holds: the Challenges of Molecular Pathology

The use of new technologies, such as next generation sequencing, which allows millions of DNA sequences to be read within a relatively short time span, is exponentially increasing the knowledge about the molecular characteristics of cancer. Moreover, the International Cancer Genome Consortium (ICGC) aims to obtain a comprehensive description of genomic, transcriptomic (RNA) and epigenomic (e.g. DNA methylation) changes in 50 different tumour types within the next five to ten years. This unprecedentedly detailed information will, undoubtedly, significantly enhance our knowledge of cancer and our approach to its treatment. As more information and technology become available, expertise in systems biology (where the interactions between components of a biological system are studied to understand how these give rise to the function and behavior of that system) and the management of the vast amounts of complex information will come in to play. This new wealth of data can then be incorporated into the delivery of personalised cancer diagnosis and the development of highly effective therapies.

As these new targeted drugs are developed and tested in clinical trials, the laboratory analysis of molecular biomarkers, which reveal disease response, will have to develop dynamically if we are to deliver truly individualised cancer treatment. In the form of the Centre for Molecular Pathology, The Royal Marsden and the ICR will have one of the leading international resources to realise this ambition.

**Figure 2**  
Analysis of *HER2* Expression and Copy Number in Gastric Cancers

- Gastric carcinoma immunohistochemically stained for *HER2* with a strong positive (3+) result indicating probable response to Herceptin. Brightfield dual colour *in-situ* hybridisation (BDISH) isn't required.
- Another gastric cancer showing an equivocal 2+ result – this requires BDISH to determine whether the gene is amplified or not.
- BDISH in a case with amplification of the *HER2* gene (as in Figure 2A). Grains labelled with a silver signal (shows as black) identify *HER2*, and vastly outnumber the control red grains (chromosome centromeres). This shows that only the *HER2* genes, and not the chromosomes that contain the genes, are amplified.
- BDISH in an unamplified case, with equal numbers of red and black grains up to a maximum of two each per nucleus.



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**Professor Steve Webb**

PhD DSc DIC FIPEM FInstP FRSA CPhys CSci

Head of the Joint Department of Physics,  
The Institute of Cancer Research and  
The Royal Marsden.



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## A Bright Future for Physical Techniques in Radiation Therapy

*“The infrastructure of our Physics Department brings together research physicists, clinical physicists and clinical implementers.”*

— Professor Steve Webb

## A Bright Future for Physical Techniques in Radiation Therapy

Professor Steve Webb PhD DSc DIC FIPEM FInstP FRSA CPhys CSci

Radiation therapy generally uses high-energy X-rays of a few million electron volts targeted to the tumour in order to break double-strand DNA, and thus damage tumours irreparably. Because X-rays have to pass through normal organs and structures in the body en route to their target, some collateral damage may occur in such structures. The goal of radiation therapy is to cure the tumour whilst minimising the dose to these other tissues. This goal has not changed since the first radiation therapy treatment was performed in 1896, just one year after the discovery of the X-ray itself. However, the methodology by which the goal may be achieved has dramatically changed in recent years. Two developments have been of seminal importance. The first has been the development of collimator technology; this enables a geometrical shaping of the radiation beam to the projected shape of the target. The second has been the development of so-called intensity-modulated radiation therapy (IMRT), by which the pattern of radiation across the beam aperture is varied as a function of position.

### From Concept to Commercial Implementation

Up until the late 1980s, no one had seriously considered the possibility of multileaf collimator technology or IMRT. Research carried out in the early to mid 90s in the Joint Department of Physics (and elsewhere), led to the rapid development of techniques to both plan and deliver IMRT. By the year 2000, commercial manufacturers were implementing our concepts and producing equipment that was ready for clinical use. The achievement in the last decade has been to both further develop and roll out this technology to a wider number of hospitals and also, most importantly, to conduct clinical trials to demonstrate level-one evidence of its efficacy.

### Real Clinical Benefit

Initial groundwork carried out at The Royal Marsden and the ICR has led to many successful clinical trials, some of which are highlighted here. Professors John Yarnold from the Section of Radiotherapy and Phil Evans from the Joint Department of Physics carried out a Phase III trial comparing IMRT with standard 2D radiotherapy. They found that breast IMRT led to a reduction in cardiac and lung damage, as well as better preservation of the treated breast compared with the 2D radiotherapy. The collaborative research of Dr Carl Rowbottom (now at Christie Hospital NHS Foundation Trust, Manchester), Professor Steve Webb, and Dr Chris Nutting from the Head and Neck Unit, culminated in a Phase III clinical trial conducted in patients with head and neck tumours, which demonstrated that the IMRT arm was greatly superior to the non-IMRT arm in reducing damage to the salivary glands (xerostomia). Dr Chris Nutting has also demonstrated that IMRT can reduce the dose to the saliva-generating gland (parotid) in tonsil cancer compared with conventional therapy

(Figure 1). Work carried out in the Joint Department of Physics, which showed that the damage to rectum, bladder and small bowel could be spared by suitable IMRT of the prostate, is now being followed up by a program of clinical IMRT in prostate cancer led by Professors David Dearnaley and Alan Horwich from the Section of Radiotherapy. All these major clinical improvements have transformed the quality of life of cancer survivors treated with IMRT. In principle, for equivalent collateral damage, tumour control is predicted to increase.

### The Marriage of Imaging and Therapy – the Motion Problem

There are currently two major limitations to the success of clinical IMRT. The first is that the target volume determined by X-ray computed tomography may not tell the whole story, and the second is related to tumour movement.

To address the first problem, Dr Mike Partridge from the Joint Department of Physics is capitalising on functional imaging to guide radiation therapy using radioisotope images as well as magnetic resonance imaging, in conjunction with Professor Martin Leach and his team.

The second limitation – tumour movement, specifically respiratory motion – is particularly relevant in the treatment of lung cancer. Over the years, we have studied the characteristics of these motions and we are now on the point of developing techniques to track targets in real time, and to feed back this knowledge into controlling the accuracy of the radiotherapy. One technique is known as ‘gating’, whereby the radiation is only switched on when the target is in a specific position. The second method is ‘tumour tracking’, whereby the radiation follows the path of the motion so that in the

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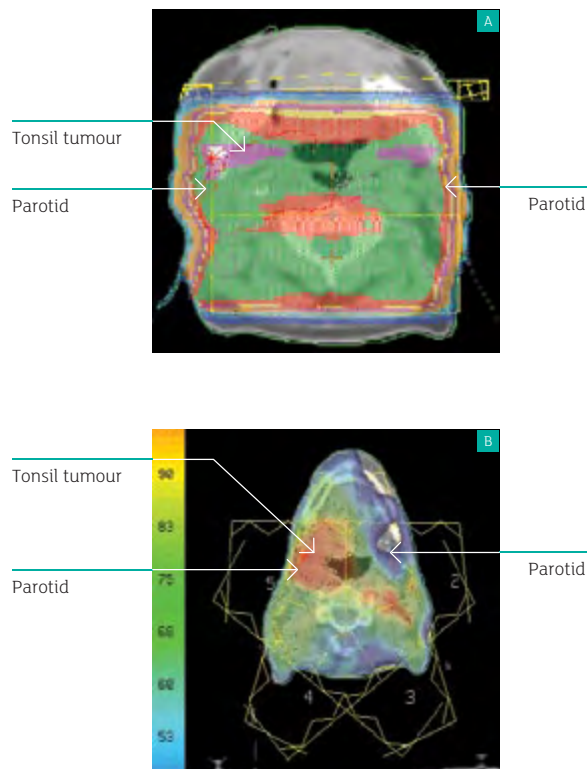
*“Recent IMRT clinical trials, conducted at The Royal Marsden, have shown improved normal tissue sparing compared with non-IMRT therapy during the treatment of breast, prostate, and head and neck cancers.”*

frame of reference of the radiation, the target is pseudo-stationary. A third technique, known as ‘breath hold’, is already in use. This is where patients can be trained to hold their breath in specific geometrical configurations for a limited period of time whilst the radiation is delivered.

To track tumour movement, we are using the Calypso system of radio beacons to follow the motion of the target in real time. This information is collected and is used to guide motion-corrected radiation therapy. We are the first centre in the UK to use this technique and, even though this work is in its infancy, Professor Mike Brada from the Section of Radiotherapy is now leading research on adapting this promising technique for lung tumours.

**Figure 1**  
Intensity-modulated Radiation Therapy –  
Reducing the Dose to the Saliva-generating  
Gland (Parotid) in Tonsil Cancer

- A. Conventional (non-IMRT) radiotherapy of a tonsil tumour gives too high a dose to both of the parotids.
- B. By choosing a set of IMRT fields, appropriately arranged around the patient, the dose (represented by a colour scale) to the parotid is reduced enough to maintain saliva generation after successful radiotherapy.



**Biological Outcome**

When a patient presents at a hospital, they wish to be cured of their cancer with minimum side effects. The doctor translates this into maximising their tumour control probability (TCP) with minimal normal tissue complication probability (NTCP), and it is the physicist who translates this information into the language of dose delivery. The methods of relating dose to TCP and NTCP are themselves the subject of intense research activity. Dr Mike Partridge and his team are trying to correlate the spatial distribution of dose to normal structures with the observed clinical outcomes seen in radiation therapy trials. This is difficult work but is proving promising, such that it might be possible to design dose distributions tailored to minimum side effects.

**The Future**

It is largely unknown how to tailor radiation therapy individually to the patient other than coping with their individual geometry. However, the understanding of the human genome may in future enable a far more comprehensive planning process that takes into account the individual radiosensitivities of each patient and other genetic and biochemical characterising information. Unfortunately, there is always an inevitable gap between what physicists are able to demonstrate theoretically and what can be implemented in practice, owing to regulatory and commercial processes.

Finally, it is the synergistic integration of imaging and radiation therapy that is likely to lead to long-term progress. In the light of this, we have established a Cancer Imaging Centre, led by Professors Martin Leach and Nandita deSouza. This will provide the framework for imaging that will continue to enable improvements in radiation therapy physics.

**Volumetric Modulated Arc Therapy (VMAT) – a New IMRT Technique**

In this technique, as the radiation beam rotates around the patient, the shape of the beam, its brightness and the speed of rotation can all be varied. Studies by Dr James Bedford from the Joint Department of Physics, in collaboration with the company Elekta Ltd, have shown that VMAT gives similar dose distributions to other IMRT methods, but has an improved treatment time for most tumour sites. This translates to a greater patient throughput – vital in all cancer treatment economies – and might also lead to the generation of fewer secondary cancers compared with other IMRT therapies. Our team has been pioneering techniques to both plan and deliver VMAT, and we have also expended much effort on trying to understand the physics of what may generate this improved benefit – a concept not immediately obvious.

## Clinical Trials

Our clinical trials units are internationally renowned for conducting Phase I, II and III clinical trials.

In this section, we hear from the patient's perspective how colorectal and ovarian cancer trials, conducted at The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, have made an impact on their lives.

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*KRAS* gene mutations as biomarkers in colorectal cancer – Mark Watson's Story  
Dr Ian Chau

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PARP Inhibitors in Ovarian Cancer – Julie Balkwill's Story  
Isobelle Coombes





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**Dr Ian Chau MD FRCP**  
Consultant Medical Oncologist,  
The Royal Marsden.



Mark Watson is a 44-year-old police support worker taking part in a trial evaluating a novel combination therapy in colorectal (large bowel) cancer. The global trial, led by Professor David Cunningham at The Royal Marsden NHS Foundation Trust (The Royal Marsden), began in February 2008, with the aim of investigating the efficacy of using the antibody treatment cetuximab, and irinotecan, in combination with a further antibody, dalotuzumab. In selection for the study, patients were tested for a mutated *KRAS* gene, as those who test negative for this biomarker show a greater response to treatment with cetuximab, allowing the trial to focus on patients who are more likely to benefit from the novel therapy.

Cetuximab is an antibody treatment that targets Epidermal Growth Factor Receptor (EGFR). This antibody was licensed worldwide in 2004 following a pivotal trial in colorectal cancer patients, led by Professor Cunningham at The Royal Marsden, in which the combination of cetuximab and irinotecan was found to circumvent tumour resistance to irinotecan chemotherapy alone. Since cetuximab has become available, further translational research has focused on investigating why certain patients do not benefit from the drug. These studies have shown that in around 40% of all advanced colorectal cancers, the tumour cells harbour a mutation of the *KRAS* gene, which prevents patients benefiting from anti-EGFR antibodies such as cetuximab. It is now routine clinical practice to test patients' tumours for the *KRAS* mutation before they are offered treatment with anti-EGFR antibodies. This refinement of patient selection has spared many patients worldwide unnecessary and potentially toxic treatment.

The novel element of the current trial is the use of an antibody treatment that targets an insulin growth factor receptor (IGFR) called dalotuzumab (MK-0646). In preclinical models, dalotuzumab has shown to provide enhanced benefit when combined with cetuximab.

Mark was 41-years-old when he was diagnosed with colon cancer in Devon, in December 2006. He originally underwent surgery to remove his colon cancer and received subsequent chemotherapy to prevent the cancer returning. Unfortunately by September 2007, there was evidence of relapse in his liver and peritoneum and he received a second course of chemotherapy for another six months, finishing in April 2008. By October of the same year, his cancer had grown further in his liver and peritoneum and he was changed to a third chemotherapy regimen. In August 2009, his cancer grew yet again and there were no longer any established treatment options available at his local hospital. At this point, his tumour was found to be negative for the *KRAS* mutation, putting him in the group of patients who might potentially benefit from an anti-EGFR antibody like cetuximab.

Since starting his trial treatment in December 2009, Mark has encouragingly had shrinkage of the secondary disease in his liver and peritoneum, where his tumour had previously shown a repeated resistance to chemotherapy. Although Mark has suffered from many of the recognised side effects of this therapy, so far his continued treatment in the trial has maintained the tumour shrinkage.



## PARP Inhibitors in Ovarian Cancer – Julie Balkwill’s Story



Julie Balkwill, a mother of two from London, is taking part in a trial of a completely novel form of treatment for ovarian cancer, involving a class of drugs called poly (ADP-ribose) polymerase (PARP) inhibitors. The trial, which started in 2007, involved almost 100 patients, about half of whom had ovarian cancer linked to mutations of the *BRCA2* gene. The trial is based on key observations made at The Institute of Cancer Research (ICR) by Professor Alan Ashworth’s group, who predicted that patients with *BRCA*-associated cancer would be particularly sensitive to PARP inhibitors. Our results from the trial have proved to be so promising that PARP inhibitors from numerous pharmaceutical companies are now being assessed in a large number of randomised trials.

Julie, aged 54 years, was initially diagnosed with advanced ovarian cancer, having presented at Kingston Hospital in April 2002 with shortness of breath and swelling of the abdomen. This was due to the accumulation of fluid in the lining of the lungs and in the peritoneal cavity resulting from the spread of cancer from a large mass in the pelvis – this proved to be a primary ovarian cancer. After surgery, she was transferred urgently to The Royal Marsden, where she received chemotherapy with carboplatin and paclitaxel. Over the next five years, she received various types of chemotherapy on four separate occasions, with the intervals between courses steadily decreasing. When patients such as Julie have repeat responses, there is a higher chance that their cancer has an underlying *BRCA* mutation. We therefore carried out *BRCA* testing on Julie, and since this proved positive for a germline mutation of *BRCA2*, we were able to discuss with her the treatment option of olaparib, a PARP inhibitor from AstraZeneca (initially KuDOS). Her treatment with olaparib was initiated in July 2007, when there was clear evidence of disease progression, along with increasing abdominal pain.

Julie was one of the first patients with ovarian cancer ever to receive olaparib. As we have seen with most patients, she tolerated the drug very well. From her point of view, there was no doubt that the treatment was “a great deal easier than receiving chemotherapy”. Within three months, it was clear that her treatment was helping, as her pain disappeared, and improvements were seen in terms of her Computed Tomography (CT) scan and a fall in CA125, a protein which is elevated in ovarian cancer.

Over three years later, Julie is still in remission as a result of her continued treatment with olaparib. Julie has recently enjoyed holidays in Spain and Qatar.

## Beyond Research

In this section, we focus on our industry partnerships, academic highlights and the education of the next generation of cancer researchers.

Dr Susan Bright highlights the important work that our Enterprise Unit carries out, working with scientists to maximise the commercial potential of inventions through establishing industrial collaborations. We interview Simon Powell, one of our alumni, who is now based at the prestigious Memorial Sloan-Kettering Cancer Center and Nicole Simonavicius, one of our current students, tells us about her experiences as a PhD student at The Institute of Cancer Research.

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[Academic Dean's Report](#)

Professor Alan Horwich

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[Technology Transfer Report 2009/10](#)

Dr Susan Bright

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[Educating the next generation of cancer researchers and clinicians](#)

Nicole Simonavicius







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## Technology Transfer Report 2009/10

*“The Enterprise Unit works with scientists from The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research to identify inventions with commercial potential and establish industrial collaborations to exploit these inventions. Commercial partners provide the resources to develop our novel ideas, thus ensuring that as many patients as possible benefit from the discoveries we make.”*

— Dr Susan Bright

The main purpose of the Enterprise Unit, which was established in November 2000, is intellectual property management. This means that the Enterprise Unit is responsible for all material transfer agreements, confidentiality agreements, collaborations with industry and technology licensing. The Unit is responsible for the formation of spin-out companies and provides these companies with support, and will also assess inventions for patenting and oversee the filing, prosecution and maintenance of The Institute of Cancer Research's (ICR) patents. Here Dr Susan Bright, Director of the Enterprise Unit, provides us with some of the Unit's highlights of 2009/10.

#### New Patents

In 2009/10 the ICR was involved in several new patent filings. Of particular note is the patent relating to the novel Magnetic Resonance Imaging (MRI) coil designed by Professor Nandita deSouza's team under their recently awarded Medical Research Council (MRC) translational grant. The novel coil, specially designed for imaging the cervix, is the first of its kind to be developed for use with the higher magnetic field strength MRI systems that are now available.

#### Faringdon Fund

The Faringdon Fund was established by the ICR in 2006 at the suggestion of Lord Faringdon, a former Chairman of the ICR. This fund bridges the gap between research funding and full commercial funding. The money is used to develop inventions that arise from research to a point where they are more likely to be taken up by industry. One of the functions of the Enterprise Unit is to manage the Faringdon Fund process and in 2009/10, several awards from the fund were made:

- Dr Glenn Flux of the Joint Department of Physics to develop treatment planning software for targeted radionuclide therapy, enabling better decisions to be made about doses to be administered (Figure 1).
- Dr Faith Davies of the Section of Haemato-oncology to develop an endoribonuclease assay for a high throughput drug screen. This will enable the team to develop drugs against a novel target that is predicted to be important in multiple myeloma.
- Professor Martin Leach of the Cancer Research UK and Engineering and Physical Sciences Research Council (EPSRC) Cancer Imaging Centre to study distortion correction in MRI, enabling improved interpretation of MRI images.

#### New Industrial Collaborations

In 2009/10, Royal Marsden and ICR scientists began a number of new collaborations with industry, some of which are highlighted below. The Enterprise Unit sets up the contracts that govern these, and often plays a key role in managing the commercial aspects of the relationship once the collaboration is underway.

#### MerckSerono – WNT Pathway

In 2009, the ICR began a major collaboration with the German pharmaceutical company MerckSerono to discover novel drugs targeted at a series of enzymes, known as the WNT pathway. The WNT signalling pathway plays a role in developmental processes including cell proliferation and cell polarity. Therefore, an overactivation of this pathway can play a key role in tumour development. At the ICR, the project is led by Professor Julian Blagg, Deputy Director of the Cancer Research UK Cancer Therapeutics Unit; the University of Cardiff is also involved under the leadership of Professor Trevor Dale, who initiated these studies when he was working at the ICR in the Section of Cell and Molecular Biology. MerckSerono provides financial support for the ICR and Cardiff teams, but also contributes its own resources and expertise. The team hopes that, by combining the strengths of all the parties, significant progress can be made against this difficult cancer target.

#### Synthetic Lethality

Professor Alan Ashworth's team at the Breakthrough Toby Robins Breast Cancer Research Centre at the ICR have developed innovative methods to analyse how cancer drugs will perform in cancers with different genetic mutations.

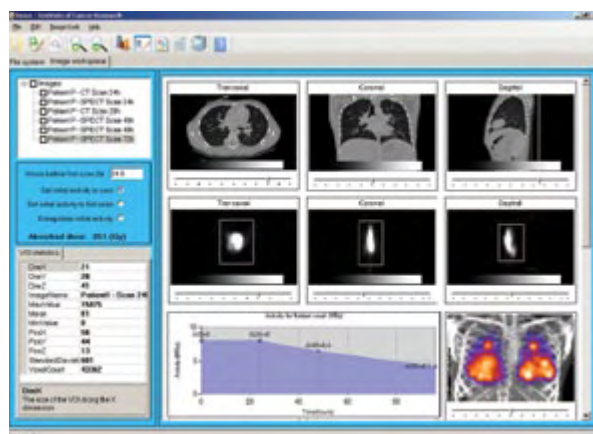
It is clear that new drugs can be used a lot more effectively if it is understood which patients will respond and which will not: this is the approach taken by 'personalised medicine'. Professor Ashworth's approach looks for synthetic lethality – combinations of defects that appear to be harmless in isolation but together are lethal to the tumour cell. The team can do this in a high throughput and comprehensive way, leading to a rapid generation of useful results. This capability has attracted a lot of attention from potential industrial partners, and a number of collaboration agreements have been set up over the past year with many different important oncology companies.

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*“It is clear that new drugs can be used a lot more effectively if it is understood which patients will respond and which will not: this is the approach taken by ‘personalised medicine.’”*

**Figure 1****Screenshot of internal dosimetry program qDose**

qDose is a new program developed at the ICR that calculates how doses of treatment are being absorbed by a patient over time. The left-hand panel is a user interface for data input and output. The image panel displays Computed Tomography (CT) (top) and Single Photon Emission Computed Tomography (SPECT) (middle) data. The program uses activity-time curves to calculate and display fused absorbed dose maps (bottom).



### Megavoltage Computed Tomography (CT) Imaging During Advanced Radiotherapy Treatment

Investigators from The Royal Marsden and ICR Radiotherapy Physics teams, under the direction of Professor Steve Webb, have demonstrated the feasibility of obtaining good quality cross-sectional images during radiotherapy delivered using advanced techniques. The work, led by Drs Gavin Poludniowski and Michael Thomas, has attracted the interest of one of our existing industry partners, Elekta Ltd, who are collaborating with us to further evaluate our CT reconstruction technology with a view to integration into commercial imaging products.

### Industrial Partners Make Progress

After an industrial collaboration is completed, the industrial partner usually takes the technology that has been developed with The Royal Marsden and ICR and progresses it further through clinical trials and then to the market. The Royal Marsden and ICR will often receive payments from the partner as significant stages of development are passed; once the product is in the market, we will also receive a royalty income. It is the job of the Enterprise Unit to monitor progress of these products and to liaise with the licensee, to ensure that The Royal Marsden and ICR receive the income that is due to us. We are always delighted of course, to hear that our own products are progressing satisfactorily.

Over 2009/10, some major milestones were reported to us. In particular, the novel heat shock protein (HSP) 90 inhibitor that the ICR developed together with Vernalis, now licensed to Novartis, has entered Phase II clinical trials. HSP90 is a 'molecular chaperone', which is involved in the folding and activity of cancer-causing proteins, and research has shown that silencing this protein can stop tumours growing. Also the novel Protein Kinase B (PKB) inhibitor that the ICR developed together with Astex, now licensed to AstraZeneca, has been selected by the company to enter Phase I clinical trials. PKB regulates proliferation, angiogenesis and programmed cell death – three cellular activities often found deregulated in cancer.

### Awards from the Wellcome Trust and Medical Research Council

Many 'not for profit' organisations provide grants for translational research projects that build on academic discoveries and have the specific objective of delivering a product that can be licensed to an industrial partner. University technology transfer offices, such as the Enterprise Unit at the ICR, are expected to participate in the grant application process for these sorts of award, providing information about the commercial potential of the technology, the patent status and the competition. The Enterprise Unit has contributed to a number of these applications, and in the past year we can record two notable successes. Professor Alan Ashworth's team at the ICR, working in collaboration with a number of other Royal Marsden and ICR scientists, was successful at winning a Seeding Drug Discovery Initiative award from the Wellcome Trust to work on the drug target tankyrase. Professor Nandita deSouza's team at The Royal Marsden and the ICR was successful in winning an MRC Development Pathway Funding Scheme award to develop and optimise advanced Magnetic Resonance (MR) imaging techniques for improved detection of small cervical cancers.

### Clinical Trial Agreements

In 2009/10, the Enterprise Unit was responsible for negotiating the agreements for over 70 clinical studies. In some cases, particularly with multi-centre studies, many agreements need to be put in place just for one study.



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## Academic Dean's Report

*“The Institute of Cancer Research celebrated its Centenary in 2009, and the joint institution has had another successful year of academic events and achievements.”*

— Professor Alan Horwich

## Academic Dean's Report

Professor Alan Horwich PhD MRCP FRCR FMedSci

The Institute of Cancer Research (ICR) celebrated its Centenary in 2009, and together with The Royal Marsden NHS Foundation Trust (The Royal Marsden), we have had another successful year of academic events and achievements. We congratulate our appointed Professors and Readers, graduating research students, and those involved in our successful bid to the Medical Research Council (MRC) for a Doctoral Training Centre in Molecular Pathology and Integrative Medicine.

### Academic Titles

The achievements of our senior scientists and clinicians continue to be recognised by the conferment of academic titles of the University of London. During the period covered by this Report, Pascal Meier became Professor of Molecular Cell Biology, Ros Eeles became Professor of Oncogenetics, Stephen Johnston became Professor of Breast Cancer Medicine, Jorge Reis-Filho became Professor of Molecular Pathology, Phil Evans became Professor of Medical Radiation Physics, Johann de Bono became Reader in Experimental Cancer Medicine, Jeff Bamber became Reader in Physics Applied to Medicine and Kevin Harrington became Reader in Biological Cancer Therapies.

### Centenary Conference

In June 2009, the ICR held a three-day conference on the theme of 'Cancer Genes: Discovery and Exploitation' at the Queen Elizabeth II Conference Centre in Westminster, London. Opening the conference, Professor Peter Rigby, Chief Executive, gave a fascinating and informative historical overview of the ICR's first 100 years. Scientists from the ICR presented their work, alongside eminent external speakers from all over the world. There were two keynote lectures given by Professor Sir David Lane, Director of the Cancer Research UK Cell Transformation Research Group at the University of Dundee, and Professor Alan Hall, Chair of Cell Biology at the prestigious Memorial Sloan-Kettering Cancer Center in New York. A poster exhibition was also held at the conference, enabling ICR students to showcase their work.

### Award Ceremony

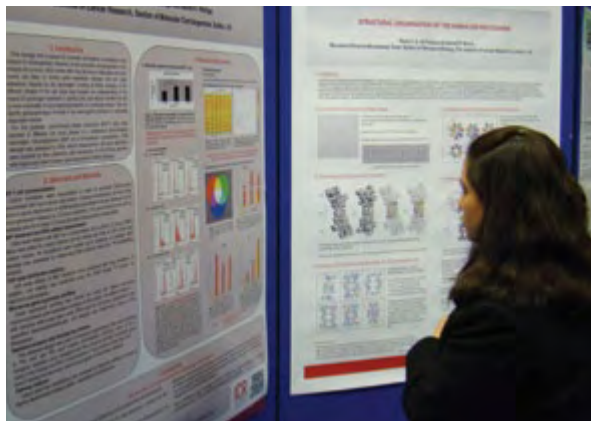
The 2009 Award Ceremony was held in November at the University of London. Eighty-seven graduates received their University of London degrees; 24 gained the Doctor of Philosophy (PhD), nine received the Doctor of Medicine (MD), four received the Doctor of Medicine (Research) (MD(Res)) and 11 received a Master of Science (MSc). Postgraduate Diplomas and Certificates in Oncology were awarded to a further 20 students. The Chairman's Prize for the two outstanding graduating PhD students was awarded to Dualta McQuaid and Paulo Ribeiro.

Last year, in honour of the ICR's Centenary, five honorary degrees were conferred. Professor Alan Hall MA PhD FRS FMedSci was at the ICR from 1981 to 1993 and did much to bring about the molecular biology revolution that was essential for the ICR's scientific development at the time. He was conferred for his pioneering contributions to cell biology research and its application to the study of cell motility in cancer progression. Professor Jacques Miller MB PhD DSc FAA FRS, who was at the ICR from 1958 to 1966, was conferred for having discovered the immunological function of the thymus, and for his identification of the T and B cell subsets of lymphocytes and determining their function. Professor Robert Souhami CBE MD FRCP FRCR FMedSci was conferred for his outstanding services to the training and practice of Medical Oncology. Following a career in the civil service, culminating in appointment as Permanent Secretary of the Department of Health & Social Security (1981-87), Sir Kenneth Stowe MA GCB CVO was an ICR Trustee and Chairman between 1987 and 1997 and is the first non-scientist to be honoured by the award. He was conferred for his incomparable service to healthcare and medical research, and in particular to the furtherance of cancer research. Professor Ian Tannock MD PhD FRCPC, who undertook a PhD at the ICR in 1965, was conferred for his distinguished and influential contributions to translational and clinical research and its application to patient-centred oncology practice.

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*"The programme of lectures for 2010 began with Dr Mariano Barbacid, Director of Centro Nacional de Investigaciones Oncológicas in Madrid, Spain, speaking on 'Targeting RAS pathways in cancer'."*

Student posters on display at the ICR Centenary Conference



### Medical Research Council PhD Programme

Following a competitive bidding process, the ICR has been awarded funding from the MRC for a new PhD programme. The programme in Molecular Pathology and Integrative Medicine will build on existing strengths in cell and molecular biology, structural biology, systems biology and molecular pathology. Projects will be co-supervised by Principal Supervisors from two different subject areas, and students will undertake leading-edge research in a translational setting directed towards cancer. They will benefit from an environment that includes first-rate basic research driving a molecular level understanding of cancer, facilities and expertise for high-throughput descriptive and functional molecular pathological characterisation of tumours, and an ethos of laboratory-based and clinical researchers committed to working together with the aim of patient benefit from the development of novel therapies. The first students funded by this programme will join the ICR in October 2010.

### Distinguished Lectures

The ICR held a special series of Distinguished Lectures as part of its Centenary celebrations. These included Dr Richard Treisman, Director of the Cancer Research UK London Research Institute, who gave a lecture on “MAL: Linking the actin cytoskeleton to the transcriptional regulation” and Professor Suzanne Cory from the Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia, who spoke on “The Bcl-2 family: An Achilles heel for cancer?”. Professor Andrew Hamilton, Vice Chancellor at Oxford University (prior to October 09 was Provost, Yale University, USA), brought his insight on “Synthetic approaches to the disruption of protein-protein interactions involved in oncogenesis” and Dr Jim Smith, Director of the MRC National Institute for Medical Research, spoke on “Mesoderm induction revisited”.

The programme of lectures for 2010 began with Dr Mariano Barbacid, Director of Centro Nacional de Investigaciones Oncológicas (CNIO) in Madrid, Spain, speaking on “Targeting RAS pathways in cancer”.

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**Nicole Simonavicius**

4th year PhD student at the Breakthrough  
Toby Robins Breast Cancer Research  
Centre, The Institute of Cancer Research.



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## Educating the Next Generation of Cancer Researchers and Clinicians

*Our 'bench to bedside' approach is mirrored in the way we nurture young scientists into the next generation of cancer experts. We have an excellent reputation for developing Postgraduate students and Clinical Research Fellows, with members of our alumni now leading academic departments and prominent cancer research organisations.*

## Our Alumni

### Simon Powell



Simon Powell is Chair of the Department of Radiation Oncology at the Memorial Sloan-Kettering Cancer Center in New York. He started his clinical training in oncology in 1984 with The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research and in 1988 he became a PhD student in

DNA repair and double-strand break repair mechanisms. He came back to the ICR in the summer of 2009 to give a Distinguished Lecture on understanding the connections in the BRCA1-BRCA2 pathway of homologous recombination.

#### What did you enjoy most about working at The Royal Marsden/ICR?

I really enjoyed the collaborative atmosphere and the clear focus on cancer research and treatment.

#### How did your time at The Royal Marsden/ICR affect your future interest in cancer research?

The research work I started at the ICR has shaped my career. I started in DNA double-strand break repair, and I am still working in this field.

#### What advice would you give to a newly qualified cancer researcher?

You need to train well, seek the best mentors, be enthusiastic, and have enormous energy. What this really means is: be well equipped to handle rejection of your first grant, your brilliant paper submitted to *Nature* or *Cell*, or your wonderfully conceived experiments that end up not working. One or all of these things will happen to everyone at some point in their life, even Nobel Prize winners.

#### What do you find most interesting about your current work?

My work covers the full spectrum of research from basic biology to translational applications. Having the interplay between basic science and how it might apply to human cancers adds an extra dimension to the work in the laboratory.

#### What would you change about your current role?

Not much. I lead a department at one of the best cancer centres in the world and I do the work I want to do.

#### Would you change any of your career choices since leaving The Royal Marsden/ICR?

For a clinical scientist, the dilemma is always how much of the science do you lose by having an active clinical role. Conversely, if you lose touch with real clinical questions, how can science and clinical progress stay hand-in-hand? I have always strived to make the role of a clinical scientist a viable entity in the modern world of research, but it is a difficult balance.

#### What do you think of the collaborative 'bench to bedside' approach adopted by The Royal Marsden/ICR?

One of the greatest challenges of current academic medicine is creating an infrastructure in which bench to bedside research becomes the norm. It is one of the goals that I strive for, and encourage from members of our department.

#### How do you think 'Personalised Medicine' will change the future of cancer research?

This topic is already at the front and centre in the current thinking. Targeting DNA repair deficiency in cancer may represent a potential Achilles' heel in cancer, which can be exploited by individually tailoring treatment approaches.

#### What do you think has been the biggest breakthrough in cancer research in the last year (2009/10)?

The continued success of biologically-rational targeted therapies – from B-Raf inhibitors for melanoma, to PARP inhibitors for breast and ovarian cancers arising in *BRCA1/2* mutation carriers, and many others in the clinical translational pipeline. The key to success is continuing to refine patient selection criteria for biologically targeted therapies.

#### What are you excited about with regard to the future of cancer research?

We will soon begin to understand the extensive information we are gathering on the collective abnormalities in cancer cells. However, I think the interface between 'omics' – systems biology studies, such as genomic and proteomic studies – and functional biology, still has a long way to go. Systems biology approaches may lead to false positives, as well as interesting and unanticipated interactions. Learning how to marry good functional biology studies with the large-scale datasets will be a big challenge, but could lead to many novel discoveries if managed optimally.

#### What do you think are the biggest challenges facing the field of cancer research?

A major challenge will be maintaining good funding sources in a time of economic difficulties. Outside of funding, the challenges are establishing real functional understanding of omic studies in the profiling of human cancers. Maintaining good quality data and a balance in the type of studies conducted is essential to our understanding of cancer, as supporting the latest fashions in cancer research is not always a good idea in the long run.

#### What do you enjoy doing outside of your research?

I try to keep my golf game in shape and our family are keen on both theatre and film.

## Our Students

### Nicole Simonavicius

Nicole Simonavicius is coming to the end of her final year as a PhD student with The Institute of Cancer Research. She joined the Molecular Cell Biology Team at the Breakthrough Toby Robins Breast Cancer Research Centre, after studying Biology at the University of Regensburg, Germany. In 2008, Nicole was awarded the Sir Antony Driver Award for outstanding contribution to Breakthrough Breast Cancer's Research, and in November 2009, her work gained first place in the European research abstract competition run by MedImmune, the global biologics unit of pharmaceutical company AstraZeneca.

#### What is your PhD project about?

My work uses pericytes, which are a type of connective tissue cell that occurs about small blood vessels, and I am particularly interested in a pericyte receptor called endosialin. I am investigating endosialin's role in angiogenesis, which is the growth of new blood vessels from pre-existing blood vessels. Endosialin has previously been shown to be upregulated on the vasculature of various different cancers. We have confirmed that endosialin is present on breast cancer and glioma (brain tumour) blood vessels but not normal blood vessels. Importantly, we discovered that endosialin is found on pericytes and not, as previously believed, on the endothelium.

#### What attracted you to study at the ICR?

During my internship in San Francisco, someone recommended the Breakthrough Toby Robins Breast Cancer Research Centre at the ICR as a good place to do research. When I looked at the website, I saw that there was a wide range of cancer research being undertaken at the ICR, tackling cancer from various different angles.

#### Do you enjoy studying within the ICR?

I do, as I like the friendly environment and the open laboratories, which foster collaborations. The students at the ICR come from all over the world, which makes it an interesting place to work.

#### Would you recommend the ICR doctoral programme to new students?

Absolutely! Students are very well looked after as they have a supervisor and an associate supervisor helping them with daily life in the laboratory. Students also have the opportunity to attend various courses and training.

#### What would you say about your supervisor and group members?

My supervisor, Professor Clare Isacke, has an open-door policy and is always there to help. My laboratory members are great. There's a very good working atmosphere, where we not only share our problems and try to help each other with experiments, but we also go out together after work.

#### How do you feel now that you are in the final year of your PhD?

As I am at the final stage of my PhD, the different pieces of my research are falling into place and it all makes sense.

#### Would you change anything about your PhD?

In the beginning, you think that with four years, you have all time in the world. However, in the end, everybody feels like they are running out of time and it can be a bit stressful trying to finish off everything! With hindsight, I would leave the experiments that are not working earlier on in the project, and move on to try a different approach.

#### What has been the highlight of your PhD?

Once I understood a bit more about the function of my protein of interest, I had a 'Eureka!' moment and looked back over old experiments that did not make sense at the time, but do now.

#### What are your future career plans?

I want to stay in research and pursue a postdoctoral position, so I can utilise all the skills I have learnt at the ICR.

#### How do you relax in your free time?

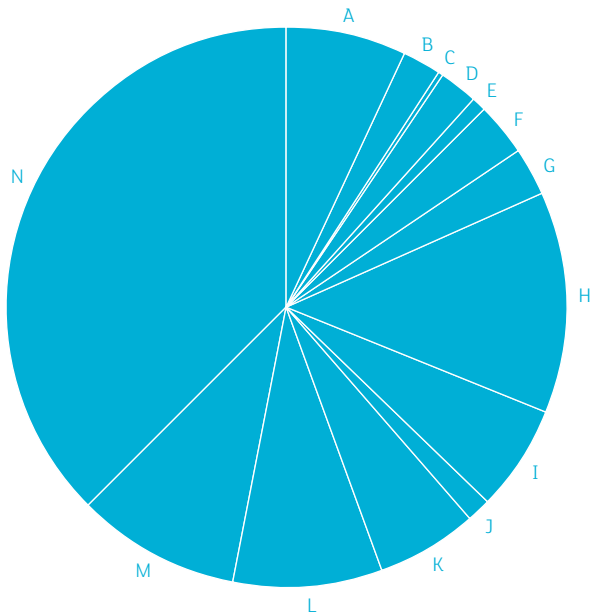
I do yoga and some running.

## Financial Summary

Our joint income has increased by £23.4m over the last financial year.

Our joint income and expenditure are shown below.

### Total income £325.7m

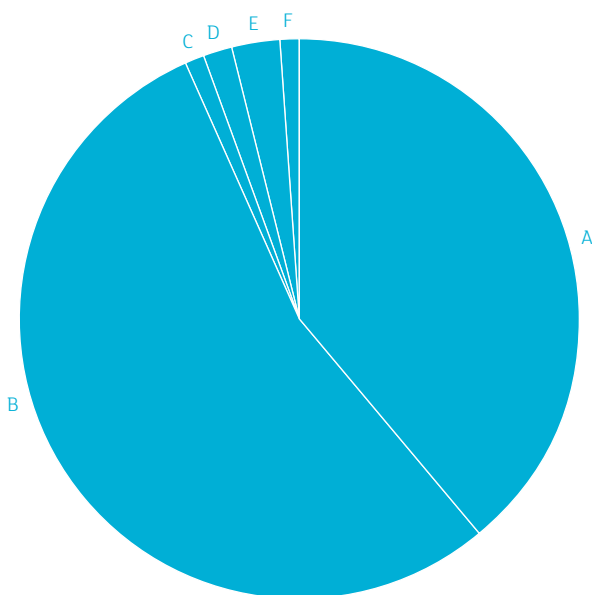


#### Summary

- Over 22% of our total research income is provided in the form of government income
- Research and Development income from the National Health Service Executive has increased by £12m compared to the previous year
- Higher Education Funding Council income has increased by nearly £2m compared to the previous year
- Income from industry and Commerce has increased over the last year due to an increased number of commercial clinical trials

- A Cancer Research UK (£23.4m)
- B Breakthrough Breast Cancer (£7.0m)
- C Leukaemia Research (£1.1m)
- D Other Charities (£6.6m)
- E Medical Research Council (£3.5m)
- F Other Government (UK, EU, US) (£9.6m)
- G Industry & Commerce (£8.6m)
- H Private Patients (£41.7m)
- I Legacies & Donations (£20.5m)
- J Investments & Property (£3.8m)
- K Other Income (inc Capital) (£19.4m)
- L Higher Education Funding Council (£28.2m)
- M NHS Executive (R&D) (£30.5m)
- N NHS (Patient Care) (£121.7m)

### Total expenditure £314.5m



#### Summary

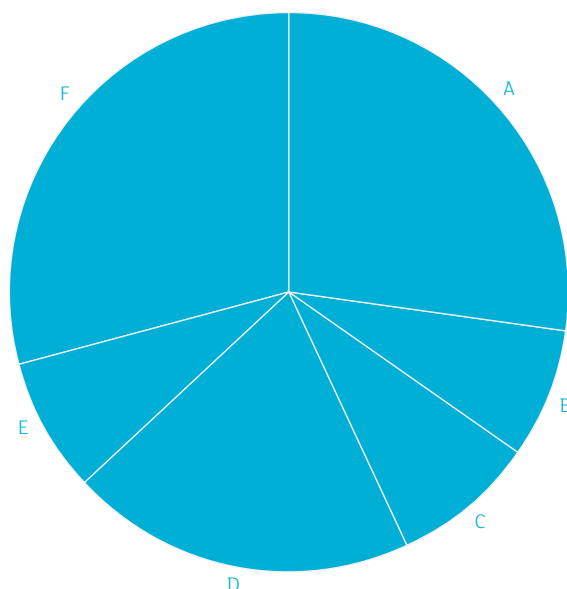
- Our expenditure on Patient Care and Treatment has increased by £24m compared to the previous year
- Over 39% of our total expenditure was spent on Research and Development, and Academic Activities

- A Research & Development and Academic Activities (£123.0m)
- B Patient Care & Treatment (£170.8m)
- C Fundraising (£3.6m)
- D Administrative Support (£5.5m)
- E Capital Development & Development Fund (£8.6m)
- F Other Expenditure (£3.0m)

## Human Resources

We have 3584 staff and 308 students across our Chelsea and Sutton sites.

Our combined human resources are illustrated below.



### Summary

- Over 36% of our staff work to support the scientific and clinical activities within our organisation; our support staff also assist our students
- Almost 30% of our total staff work in medical and nursing care
- We have 178 research and 114 taught postgraduate students; the remaining 16 students are Radiotherapy Students

		%	Number
A	Scientific, Therapeutic and Technical	27.36	1065
B	Scientific and Clinical Support	7.40	288
C	Medical Care	8.50	331
D	Nursing Care	19.84	772
E	Students	7.91	308
F	Central Support	28.98	1128
TOTAL		100	3892

Data as at the 31st December 2009.

The Royal Marsden Allied Health Professionals (AHP) and Healthcare Scientists are included in the group Scientific, Therapeutic and Technical staff.

## Research Departments

### Our Research Centres, Departments, Sections and Units

The diverse nature of our research results from the successful collaboration between The Royal Marsden NHS Foundation Trust and the The Institute of Cancer Research, allowing effective translation of laboratory research into effective patient treatments. Our research covers seven broad themes, which are categorised as shown below.

#### Cancer Biology

##### The Breakthrough Toby Robins Breast Cancer Research Centre

*Director*

Professor A Ashworth FRS FMedSci

##### Section of Cell and Molecular Biology (including the Cancer Research UK Tumour Cell Signalling Unit)

*Unit Director and Section Chairman*

Professor C J Marshall FRS FMedSci

*Deputy Section Chairman*

Professor Richard Marais FMedSci

##### Section of Gene Function and Regulation

*Chairman*

Professor P W J Rigby FRS FMedSci

##### Section of Haemato-oncology

*Chairman*

Professor M F Greaves FRS FMedSci

##### Section of Structural Biology

*Co-Chairmen*

Professor D Barford FRS FMedSci

Professor D Wigley FRS

#### Cancer Genetics

##### Section of Cancer Genetics

*Chairman*

Professor N Rahman PhD FRCP FMedSci

##### Section of Paediatric Oncology, Cancer Research UK Academic Unit of Paediatric Oncology, and the Children's and Young People Unit

*Chairman and Head of Clinical Unit*

Professor A D J Pearson MD MRCP

(UK) DCH FRCP FRCPCH

#### Cancer Therapeutics

##### Academic Department of Biochemistry

*Chairman*

Professor M Dowsett PhD

##### Breast Unit in association with the Section of Medicine

*Head of Unit*

Professor I E Smith MD FRCP FRCP

##### Cancer Research UK Cancer Therapeutics Unit, Section of Cancer Therapeutics and Clinical Pharmacology Unit

*Unit Director and Section Chairman*

Professor P Workman PhD, DSc

(Hon), FMedSci, FSB

##### Section of Clinical Trials

*Chairman*

Professor J M Bliss FRSS

##### Gastrointestinal Cancer Unit in association with the Section of Medicine

*Head of Unit*

Professor D Cunningham MD FRCP

##### Gynaecology Unit in association with the Section of Medicine

*Head of Unit*

Professor J Shepherd FRCS MRCOG

(Gold Medal) FRCOG FACOG

##### Section of Haemato-oncology

*Chairman*

Professor M F Greaves FRS FMedSci

##### Haemato-oncology Unit

*Head of Unit*

Professor G Morgan PhD FRCP FRCPPath

##### Lung Cancer Unit in association with the Section of Medicine

*Head of Unit*

Dr M E R O'Brien MD FRCP

##### Section of Medicine (including the Cancer Research UK Department of Medical Oncology)

*Chairman and Head of Department*

Professor S B Kaye MD FRCP

FRCP FRSE FMedSci

##### Section of Paediatric Oncology, Cancer Research UK Academic Unit of Paediatric Oncology, and the Children's and Young People Unit

*Chairman and Head of Clinical Unit*

Professor A D J Pearson MD MRCP

(UK) DCH FRCP FRCPCH

##### Sarcoma Unit in association with the Section of Medicine

*Head of Unit*

Professor I R Judson MD FRCP

##### Skin and Melanoma Unit in association with the Section of Medicine

*Head of Unit*

Professor Martin Gore PhD FRCP

##### Section of Surgery

*Chairman*

Professor The Lord Darzi of Denham

FRCS FMedSci FREng(hons)

#### Molecular Pathology

##### Section of Haemato-oncology

*Chairman*

Professor M F Greaves FRS FMedSci

##### Section of Molecular Carcinogenesis

*Chairman*

Professor C S Cooper PhD DSc FMedSci

##### Section of Paediatric Oncology, Cancer Research UK Academic Unit of Paediatric Oncology, and the Children's and Young People Unit

*Chairman and Head of Clinical Unit*

Professor A D J Pearson MD MRCP

(UK) DCH FRCP FRCPCH

#### Imaging Research and Cancer Diagnosis

##### Department of Histopathology

*Head of Department*

Dr A C Wotherspoon FRCPPath

##### Department of Diagnostic Radiology

*Head of Department*

Dr D MacVicar FRCP FRCP

##### Cancer Research UK and EPSRC Cancer Imaging Centre

*Joint Directors*

Professor M O Leach FMedSci

CPhys FInstP FIPEM FSB

Professor N M deSouza MD FRCP FRCP

##### Department of Nuclear Medicine

*Consultants*

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Dr V J Lewington MSc FRCP FRCP

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FRSA CPhys CSci

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*Head of Unit*

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##### Section of Epidemiology (including the Department of Health Cancer Screening Evaluation Unit)

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FFPH FRCPG FIBiol FMedSci

##### Cancer Research UK Epidemiology and Genetics Unit

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S Dolan MSc RGN

##### Department of Palliative Medicine and Pain

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#### Senior members of staff in attendance at Board of Trustees meetings

Mr J M Kipling FCA DCha

*Secretary of the ICR and Head of  
Corporate Services (to 12/2009)*

Mrs C Scivier MSc FCIPD MIOd

*Secretary of the ICR and Head of  
Corporate Services (from 1/2010)*

Professor C J Marshall FRS FMedSci

*Director of Research and Chairman  
of the Joint Research Committee*

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