Institution: Institute of Cancer Research

Unit of Assessment: UoA1 Clinical Sciences

a. Overview

The Institute of Cancer Research (ICR) is a postgraduate college of the University of London. In pursuit of its mission to make the discoveries that defeat cancer, the ICR employs a comprehensive range of research disciplines aimed at better understanding the causes of cancer and translating this into improvements in prevention, diagnosis and treatment. The range combines **fundamental research** into the biological basis and behaviour of cancer (submitted to UoA5: Biological Sciences) and **translational and clinical research** conducted through close collaboration with our partner hospital, The Royal Marsden NHS Foundation Trust (RM) (submitted to UoA1: Clinical Medicine). The ICR has over 1,000 staff and a total annual direct research expenditure of £75.48M; RM has over 3,850 staff and R&D expenditure of £25M. We share two London sites, in Chelsea and Sutton, which provide an outstanding environment for research and training in cancer research and together the institutions form the largest comprehensive cancer centre in Europe. In 2006, and again in 2011, we were designated as one of six NIHR Specialist Biomedical Research Centres, and the only one dedicated to cancer.

The ICR is organised into eight scientific Divisions and, to enable scientific interaction, many Faculty (academic staff) hold joint appointments across Divisions. Some Divisions are grouped around a discipline and others cover the whole spectrum of research focusing on a tumour type. Our REF submissions therefore do not strictly adhere to organisational groupings. This return incorporates the Divisions of Clinical Sciences and Radiotherapy and Imaging and the translational and clinically-focused research in the Divisions of Genetics and Epidemiology, Cancer Therapeutics, Molecular Pathology and Breast Cancer Research.

b. Research strategy (Note: numbered references in brackets refer to published outputs in REF2)

Over the period, the ICR Scientific Strategy has focused on the three themes of genetics, molecular pathology and therapeutics, underpinned by research in the biology of cancer and we have significant achievements in each theme.

Genetic basis of cancer

We have identified more than 1,000 genetic mutations associated with 17 major cancer types, including a number of significant findings paving the way for genetic screening and strategies for early detection and prevention (Eeles, Fletcher, Houlston, Mackay, Turnbull, Swerdlow, Wang). Specific examples are

- Discovery of two genetic variants, located on chromosomes 10p14 and 8q23.3, that increase the risk of bowel cancer (Houlston1). This allows identification of a group of people who are four times more likely to get bowel cancer and are candidates for intensive screening.
- Discovery of 23 genetic variations associated with an increased risk of prostate cancer; although each genetic change is only responsible for a small increase in risk, when combined they have a substantial effect (Eeles2).
- Mutations of *RAD51B*, a gene involved in repair of damaged DNA, can increase the risk of male breast cancer by 1.5 fold (Swerdlow3).

Molecular Pathology

We aim to use identified genetic and molecular alterations not only for improved diagnosis of cancer, but also to develop both prognostic and predictive biomarkers, and to identify molecular therapeutic targets. In the period we have:

- Convened the International Ki67 in Breast Cancer Working Group, who agreed that Ki67 measurement by IHC was the current assay of choice for tumour proliferation and proposed guidelines for the analysis, reporting and use of Ki67 (Dowsett3).
- Integrated information on standard pathological staging parameters with measurements of ER status and levels of Ki67 in surgical specimens to create a preoperative endocrine prognostic index (PEPI). Patients with a low pathological stage and PEPI score at surgery have an extremely low risk of relapse and are therefore unlikely to benefit from adjuvant chemotherapy. In contrast, patients with a high score had a higher risk of early relapse (Dowsett4).

- Discovered that mutation of the histone *H3F3A* drives a distinct gene expression pattern, including upregulating *MYCN*, a potent oncogene that can lead to the development of paediatric glioblastomas (Jones1).
- Led European paediatric clinical trials demonstrating that the *MYCN* gene copy number determines how aggressive a neuroblastoma will be. Tumours that do not have an increased number of *MYCN* genes can be treated by surgery alone, or with two to four courses of chemotherapy rather than 12 courses of chemotherapy (Pearson2).
- Participated in the national effort to deliver precision medicine as part of the CRUK Stratified Medicines programme. The ICR/RM is one of the three institutions to be selected as both a Clinical and Technology Hub for the programme.

Drug discovery and development

The Cancer Research UK Cancer Therapeutics Unit, in partnership with its collaborators, has discovered 7 pre-clinical development candidates since 2008, and currently has 7 compounds in clinical evaluation.

In addition we have:

- Developed an integrated cancer focused knowledge-base, canSAR, able to integrate heterogeneous genetic, biological, chemical, pharmacological and other data of clinical relevance (Al-Lazikani2).
- Discovered a mechanism through which Hsp90-dependent kinase inhibitors destabilise oncogenic kinases. The inhibitors, which compete with ATP binding to the kinases, can prevent the kinases from binding to the Hsp90 molecular chaperone system (Workman1).
- Shown that knocking out two forms of the Hsp70 protein, Hsc70 and Hsp72, selectively kills bowel and ovarian cancer cells (Workman2).
- Shown that Aurora-A activity is enhanced by phosphorylation at position 287 alone, but is suppressed when position 288 is also phosphorylated, the first example of a Ser/Thr kinase whose activity is controlled by the phosphorylation state of adjacent residues in its activation loop (Blagg3).
- Demonstrated via successful Phase I and II clinical trials that ovarian cancers with a mutated *BRCA* gene are particularly sensitive to treatment with PARP inhibitors (Kaye1, 2).
- Taken abiraterone, a drug designed and developed at the ICR, through clinical trials, leading to its worldwide approval for use in advanced castration-resistant prostate cancer (Attard1, 2, de Bono2).
- Played a leading role in clinical trials that demonstrated the effectiveness of aromatase inhibitors in breast cancer (Smith1,2,3) and that the combination of the aromatase inhibtior, letrozole, with the HER2 inhibitor lapatinib significantly improved the outcome for ER+, HER2+ patients with metastatic breast cancer (Johnston2).
- Performed a meta-analysis of all of the currently available data from trials of AIs vs tamoxifen which showed that the use of 5 years of an AI following surgery further reduces recurrence by approximately 23% relative to 5 years of tamoxifen (Dowsett1)
- Evaluated capecitabine (an oral fluoropyrimidine) and oxaliplatin (a platinum compound) as alternatives to infused fluorouracil and cisplatin, respectively, and demonstrated they were as effective for untreated advanced oesophagogastric cancer (Cunningham1).
- Shown that shorter intervals between chemotherapy treatments increases survival rates by two thirds in a high-risk group neuroblastoma group (Pearson1).
- Shown it is possible to target *MYCN* indirectly using small molecules that disrupt the interaction with Aurora-A kinase, which is critical for stabilising *MYCN* (Chesler2, Linardopoulos3).
- Evaluated drugs discovered in the CRUK Cancer Therapeutic Unit in neuroblastoma and other paediatric malignancies. CCT241736, a dual FLT3-aurora kinase inhibitor is undergoing pre-clinical development by CRUK Drug Development Office to treat adults and children with FLT3-mutated acute myeloid leukaemia.

Radiotherapy and Imaging

There have been three main areas of success in relation to radiotherapy:

1) Hypofractionation
   - Following large national trials testing hypofractionated breast radiotherapy, approximately 25,000 women per year are now treated with the START-B 15-fraction regimen over 3 weeks (total 40Gy) in accordance with 2009 NICE guidance. This schedule replaces a wide variety of pre-existing regimens, many of which involved 25 fractions delivered over 5 weeks (total 50Gy) (Bliss2, Yarnold1,2), and the 10-year follow-up confirmed these benefits (Yarnold4).
   - CHHiP is one of the largest prostate radiotherapy trials worldwide (3,216 patients). Pre-planned analysis of the first 450 patients found no clinically important differences in acute or late toxicity between the hypofractionated and standard treatment schedules (Dearnaley2, Hall2).
2) Targeted delivery
   - PARSPORT was the first randomised trial to demonstrate that using IMRT to spare the parotid glands significantly reduces the incidence of xerostomia (dry mouth syndrome) by ~50% for patients with pharyngeal cancers (Nutting1, Hall1).
3) Combined radiotherapy and chemotherapy
   - Bladder cancer patients given low doses of chemotherapy combined with radiotherapy were nearly 50% less likely to relapse with the most lethal form of the disease compared to patients given radiotherapy alone. The success of the trial could mean fewer patients need their bladder removed and provides a viable alternative for frailer patients who are too weak for surgery (Huddart1).
   - A study in men with stage IIA and IIB testicular seminoma has found that giving a single cycle of the chemotherapeutic agent carboplatin before radiotherapy can reduce relapse rates compared with radiotherapy alone, and the radiation dose and volume can be lowered, giving an effective non-toxic treatment with low risk of long-term treatment complications (Horwich3).

Other significant findings in the area of radiotherapy and imaging are:

- A demonstration of the effectiveness of non-invasive high-intensity focused ultrasound as an alternative to surgery in some patients with localised renal cell carcinoma (ter Haar1).
- A demonstration that quantitative diffusion-weighted magnetic resonance imaging can aid in early monitoring of chemotherapy efficacy in patients with metastatic ovarian or primary peritoneal cancer, since apparent diffusion coefficient (ADC) histograms obtained after the first and third treatment cycles show significant differences between responders and non-responders (DeSouza1).
- Showing that antiangiogenic agents targeting $VEGF_{165}$ can be combined with oncolytic virotherapy to overcome virus-associated problems such as delivery to target site through tumour vasculature and immune response. Manipulating $VEGF_{165}$ signalling allows tumour-associated endothelial cells transiently to support viral replication, leading to direct tumour cell lysis and triggering innate immune-mediated attack on the tumour vasculature (Harrington2).
- Development of a method to enhance the sensitivity of MR, enabling it to be used as a non-invasive method to clinically develop and evaluate novel, choline kinase-targeting anticancer drugs through analysis of (phosphor)choline levels, which are increased in malignant cells and have previously been shown to decrease after effective drug treatment (Leach2).

Other significant developments in the assessment period are: (i) in January 2011, Professor Alan Ashworth FRS succeeded Professor Peter Rigby FRS as Chief Executive of the ICR; (ii) the recruitment of Professor Markus Müschen from UCSF to the CRUK Chair of Molecular Pathology and Head of Division of Molecular Pathology; (iii) the recruitment of Professor Uwe Oelfke from the German Cancer Research Centre to lead the ICR/RM joint department of Physics following the retirement of Professor Steve Webb; (iv) the appointment of Professor Andrew Tutt as the new Head of the ICR Division of Breast Cancer Research and as Breakthrough Centre Director, whilst retaining his responsibility to lead the Breakthrough Unit at King's Health Partners, creating an opportunity to stimulate a wider "Breakthrough London" research program; (v) the recruitment of a further 12 Faculty, Career Development Faculty and Fellows to support our new strategy; (vi) the promotion of 12 Faculty/Honorary Faculty to

Professor and 13 to Reader.

Future Strategy

The central research theme for the next period will be the exploitation of advances in understanding the genomic and other biological alterations in cancer to deliver precision treatment, thereby improving patient outcomes. This brings together activities in genetics, molecular pathology and therapeutic development, including radiotherapy and imaging. Research activity falling outside the central themes has been closed down to allow for re-investment. New faculty recruitments are indicated below against relevant research areas.

Genetics and Epidemiology

Cancer genetics will continue to be important, so that we can identify individuals who have an increased risk of developing the disease, offering them preventative therapies or enhanced surveillance to ensure early detection and treatment. We have led the world in the discovery of germline alterations that influence cancer risk and aspire to do so in the future (Turnbull). We have also established a Translational Genetics Laboratory within the Division with the aim of accelerating the adoption of germline genetic testing in individuals with cancer into mainstream cancer medicine. The prevention of cancer will require an understanding of how genetics, environmental and lifestyle factors interact in determining cancer risk; these questions will be addressed within the epidemiological Breakthrough Generations Study.

Molecular Pathology

Understanding and exploiting the molecular and genetic changes that occur in tumours continues to be critical, and some stratification of patients is now essential in most clinical therapeutic trials. We plan to expand our capacity in this area and the opening of the NIHR Centre for Molecular Pathology is an important first step (Müschen, Sadanandam, Valeri). Our aim is that biopsies, both of tumour deposits and of circulating tumour cells and DNA, will become routine where they do not compromise patient safety. The immediate aim is to introduce targeted sequencing with the overall aim of introducing genome level tumour analyses into the clinic as rapidly as possible and at scale. This will be essential to monitor both the inter- and intra-tumoural heterogeneity that are major challenges in designing new therapeutic approaches.

Therapeutic Development

Arguably, we have been world leading in drug discovery and the pursuit of new and more effective therapies for cancer will continue to be a major aim. We have three initiatives to broaden the scope for target identification.

- We plan an expansion of programmes in cancer heterogeneity and evolution in UoA5. The basic principles of evolutionary biology can be applied to three distinct areas of cancer medicine: (i) causation or vulnerability; (ii) the time ordered biological development of cancer (over years) in the body; and (iii) the emergence of drug resistance.
- Discussions are taking place to create a strategic research alliance between ICR and the Genome Damage and Stability Centre (GDSC) at the University of Sussex. The aim is for ICR to help translate the research output of GDSC, and to kick start this initiative, there will be two PhD studentships dedicated to collaborative projects with the GDSC. The students will study genome stability in the context of cancer biology, with the aim of identifying and/or developing targets for drug development and therapy.
- The alterations in metabolism that are evident and increasingly understood at the molecular level in many cancers provide new molecular diagnostic and therapeutic opportunities. In 2012 we established a major new collaboration with Imperial College (IC), initially focusing on metabonomics, epigenomics and bioinformatics (Centre for Systems Oncology and Cancer Innovation (CSOCCI). The aim is to stimulate collaborative activity in these areas through the development of joint research initiatives, funding opportunities and training programmes. Both the ICR and Imperial are recruiting new team leaders, and 4 research studentships will be available each year for projects jointly supervised between ICR and IC.

We aim to increasingly move towards integrated cancer research and biomarker-driven

adaptive and hypothesis testing clinical trials (Cheang), and will therefore increase our emphasis on the discovery and development of biomarkers, including imaging biomarkers. We are improving our capability to carryout pre-clinical imaging research by building the Centre for Cancer Imaging due to open Q3 2014 (Kramer-Marek). The majority of clinical trials now incorporate functional imaging. The renewal of the CRUK/EPSRC Cancer Imaging Centre, the presence of a cyclotron at Sutton and our investment in PET including PET chemistry will be important in delivering this (Smith).

Radiotherapy and Imaging
Radiotherapy will remain a major therapeutic approach and our strategy for this modality will increasingly take account of developments in tumour biology and the incorporation of targeted systemic therapeutics as well as the underpinning physics. The new programme for Physics will have three themes: (i) management of intra-fraction organ motion, (ii) development of MR-guided Therapeutic Ultrasound and Radiotherapy, (iii) advanced treatment planning. We aim to improve outcomes for tumour types where RT is already a standard-of-care, but will also establish novel RT-based approaches for tumour sites that, thus far, have not been regarded as targets for high-precision RT (Harris, Oelfke, Nill).

Underpinning these activities, we are strengthening our structures to enable translational research:

- Following a review of the RM/ICR BRC in October 2012, improvements are being implemented in five main areas: structure, performance management, patient and public involvement and engagement, profile and infrastructure/core resources.
- The RM/ICR BRC Steering Committee now meets more frequently on a bi-monthly basis. This Committee awards project funding, review progress and provides direction to the BRC.
- A new RM Clinical Research Executive formed of the Director of Clinical Research/BRC, RM Chief Operating Officer, Associate/Assistant Directors of Clinical Research and Assistant Director of the RM/ICR BRC has been established.
- A formal system of Clinical Unit Research Leads has been introduced to provide research leadership at Unit level. The Research Lead is responsible for leading the Clinical Unit research programme, including the operational performance and governance of all clinical research that sits within the Units portfolio.

The ICR will form further strategic alliances and collaborations which enhance opportunities to conduct research aimed at improving outcomes for cancer patients. Cancer research requires expertise in a wide range of disciplines and we will work with the other universities in London to achieve critical mass in areas such as mathematics, computing, physics, chemistry and engineering. The realisation that common cancers such as breast and lung cancer represent a wide spectrum of cancer subtypes, each requiring different strategies for treatment will require access to large numbers of patients and integrated trial structures. We aim increasingly to work across the whole London population. An example of this is the London Lung Cancer Alliance which brings together three large clinical centres with their associated research programmes and includes a population base of 5 million people (see section e).

c. People, including:

i. Staffing strategy and staff development

New team leaders are recruited to reflect developing research priorities and to maintain existing strengths. All posts which become available are reviewed in detail and filled in accordance with our current strategy so as to promote a coherent research programme and, in particular, to promote inter-disciplinary research across Divisions (see section b). During the period of assessment, the ICR reviewed its research strategy. To allow for further investment in the fields of molecular pathology, genetics and genetic epidemiology, therapeutic development and radiotherapy and imaging which remain at the core, activity that fell outside of the central themes was identified and a number of teams were supported to move to other HEIs. Further, as part of their career progression, some staff have moved to senior positions elsewhere (Stratton, Director, Wellcome Trust Sanger Centre). We have therefore been able to make a significant number of recruitments.

Research career levels within the ICR are:

- Postgraduate students: complete programme and move to post-doctoral experience elsewhere (or for Clinical Fellows, progress to ACL position or return to clinical training);
- Postdoctoral Training Fellows: 3-4 year post, maximum extension to 7 years, move elsewhere after training period;
- ICR Fellows: researchers on independent fellowships and recipients of pathway to independence scheme funding starting to pursue their own research programmes;
- Career Development Faculty (CDF): independent investigators, lead their own research, acquire grants and studentships, 5 year review for transfer to non-time-limited post;
- Non-time-limited Faculty: established investigators with international reputations, entry via promotion from career development posts or external recruitment.

Externally-funded fellows are appointed either as post-doctoral training fellows, ICR Fellows or as CDF, depending upon the level of the fellowship and their prior research experience. The ICR provides a comprehensive support framework for all early career researchers through mentoring by senior research staff in their division.

On appointment, Faculty and CDF receive a package comprising: own salary, salaries for a postdoctoral fellow and scientific officer and access to PhD studentships and clinical training fellowships, together with laboratory start-up costs, including essential equipment and consumables. CDFs are mentored by their Head of Division and have a mid-term review at 3 years involving external advisers. The CDF association has regular meetings with the research leadership of the ICR. External coaches are available to research leaders at all levels. Team leader performance is monitored annually by an ICR Career Development Review group of senior staff in addition to the annual appraisal by their Head of Division.

The ICR's Learning and Development team works closely with the ICR's four researcher associations (Student, Postdoc, Scientific Officer and CDF) to implement the Researcher Concordat, and achieved EU HR Excellence in Research reaccreditation in 2013. The Researcher Associations manage their own budgets for career development and promote a range of activities including away-days, scientific conferences, training courses and careers conferences. They also inform, prioritise and help to deliver 150 individual training and career development activities at the ICR, open to all research staff including visiting researchers (4TUhttp://training.icr.ac.uk/U4T).

There is an active exchange of course places between the ICR, other HEIs, and research institutes to ensure our researchers have access to the widest possible range of training and career development opportunities. These collaborations include "The Pathway to Independence; Developing Future Scientific Leaders", an innovative residential programme developed through collaboration between the ICR, the BBSRC and the Wellcome Trust Sanger Institute. The project was led by the ICR's Researcher Development Advisor and funded by a grant from the Leadership Foundation for Higher Education. Partners include the CRUK London Research Institute (LRI), the Cancer Research UK Manchester Institute and the European Bioinformatics Institute (EBI).The programme aims to support outstanding postdocs with a proven track record of academic achievement at the point in their career when they are seeking their first independent research position and is designed to prepare delegates for the challenges associated with becoming a scientific leader (see http://training.icr.ac.uk/pathway/). Further, we have now established a Dean's Pathway to Independence Award and ICR's successful applicants to the programme have been awarded grants to pilot some of the research ideas they submitted as part of the application process. We are planning a similar event for clinician scientists, and have been liaising with the Academy of Medical Sciences with regards to this.

Evidence of how the submitting unit supports equalities and diversity

The ICR's Athena SWAN Charter Bronze Award was successfully renewed in April 2013 and half the research divisions are currently working towards Silver Awards. The ICR has committed to achieving an organisational Silver Award by 2016. Diversity training is mandatory for all new staff and students and briefings for new team leaders utilise the 'every researcher counts'

materials. The published annual equality report details key initiatives eg a review of promotion processes, improved support for parents.
(http://www.icr.ac.uk/about_us/strategic_plan/equality_and_diversity/index.shtml)

Clinical researchers
27 Category A staff are RM clinicians, directly involved in clinical and/or basic research and in delivering patient care; these staff have joint annual appraisals with ICR and RM (NHS) line managers and have protected programmed activity sessions PAs for their research in their NHS work plans. 16 of the 20 Category C staff returned in this submission are RM Consultants and Honorary ICR Faculty and 2 are Consultants at Mount Vernon. The clinical work of Clinical Fellows is restricted to a maximum of one session per week and three weeks of cover for colleagues per year; NHS clinical trainees involved in research are awarded 'ring fenced' research time. These arrangements facilitate the integration of ICR and RM staff in translational and clinical research. Such integration is promoted at all levels of the organisations. For example NHS radiographers have been restructured into research programmes that deliver both clinical and translational outcomes. Similarly, in Radiotherapy/Physics, NHS physicists, several of whom are Honorary Faculty and 2 of whom are included in this return, contribute significantly to the delivery of research. The integration is to the benefit of both research (recruiting patients, translating research findings into clinical practice) and the NHS (e.g. enabling specialised expertise in genetic susceptibility to be made available to cancer patients).

ii. Research students
Postgraduate research training is an essential activity in all areas of this submission. The environment provides a unique training experience because of the widespread use of integrated multidisciplinary teams in our translational research. We invest heavily in training activity and attract excellent graduates and postdoctoral fellows not only from the top UK Universities but also from Europe, the USA and worldwide.

Support for research students is organised on an ICR-wide basis. The Dean's team (postgraduate tutors) make regular checks on progress and resolve problems as and when they arise. There is an active student society and the students have themselves organised a buddy system for international students; help for new students in finding accommodation, and a student confidant system to provide advice. In January 2012 the QAA conducted an institutional review of the ICR, which found that the ICR meets UK expectations in all areas. The QAA review team also identified the following features of good practice: the monitoring of, and support for, research students' progress; the quality of the research environment for research students and the contribution students make to quality assurance.

The Institute has experience of, and a strong track record in, supporting research students from a wide variety of subject backgrounds and key to this is that they are provided with two e-learning resources to develop the knowledge and skills that are necessary to excel in cancer science research. "Perspectives in Oncology" is a modular e-learning website providing a basic grounding in cancer science covering subject matter such as cancer epidemiology, cancer genetics, cell biology, bioinformatics, medical physics, structural biology, cancer treatment and drug development. "Skills" is a blog-style resource giving advice in transferable skills at appropriate times throughout the four years. Themes covered include – Year 1: effective team work, time and workload management, and critical reading, as well as the broader implications of work at the ICR. Year 2: communicating research to a wider audience, scientific writing skills and referencing guidance. Year 3: thesis and viva preparation, writing style and avoiding scientific fraud. The same learning and development opportunities offered to research staff are offered to all research students, who also benefit from careers advice provided in partnership with the University of London Careers Service.

Between 2008 and 2013, competitively-won studentships were obtained from research councils (EPSRC 6, MRC 8) and UK-based medical charities including CRUK (20). The ICR also won funding for an innovative combined clinical/science Wellcome Trust PhD programme in Mechanism-Based Drug Discovery to which 28 students have been recruited during the period.

The ICR self-funds studentships (23 in the period) and has taken strategic decisions to a) fund all science students for four years to allow sufficient time to complete high-quality research projects and skills training; and b) to match stipends to those awarded by major cancer charities to ensure we attract the brightest applicants. The ICR therefore supplements external awards where necessary. The close association of ICR and RM provides an ideal infrastructure for clinical research fellows to undertake a PhD or MD as part of their medical career progression. The CRUK Centre and Wellcome Trust Programme provide funding for 5 Clinical Research Training Fellowships per annum.

d. Income, infrastructure and facilities

Every research grouping receives long-term competitive research support (in the form of Centre, Unit and programme grants) from major funders. The NIHR Biomedical Research Centre (£61.54M, 2012-2017) and the Cancer Research UK Centre of Excellence (£12.28M, 2012-2014) underpin the translational research activity of all groups. Research in this UoA benefits from funding for the following Centres and Unit: Experimental Cancer Medicine Centre, Ovarian Cancer Action Research Centre, EPSRC/Cancer Research UK Comprehensive Cancer Imaging Centre, Breakthrough Breast Cancer Centre, Cancer Research UK Cancer Therapeutics Unit. Cancer Research UK Clinical Trials and Statistics Unit, Cancer Research UK Stratified Medicine Clinical and Technology Hub.

In Molecular Pathology, Dr Zelent successfully renewed programme grant funding from Leukaemia & Lymphoma Research (£0.69M, 2009-2012; £1.43M, 2012-2017, overall grade 1.6) and Professor Morgan attained Myeloma UK programme funding (£2.58M, 2012-2016).

In Genetics and Epidemiology, CRUK renewed the two programme grants to Eeles and Houlston (£3M in total to each programme, 2012-2015; both rated Forefront/Outstanding). Houlston renewed his Leukaemia & Lymphoma Research programme grant (£1.01M, 2010-2013; £1.43M 2013-2018). Programmatic funding for the Breakthrough Generations study was secured by Swerdlow (£6.2M, 2009-2014).

Research in Radiotherapy and Imaging, which includes the department of Physics, is funded through a CRUK programme grant led by Horwich (£3.5M, 2009-2014, rated Forefront/Outstanding) and a second CRUK programme grant awarded to Harrington and Nutting (£1.12M, 2012-2017). The CRUK/EPSRC Cancer Imaging Centre, led by Leach and deSouza, was established and renewed during the period (£8.63M, 2008-2012; £7.3M, 2013-2018; rated Forefront/Outstanding).

Research in Cancer Therapeutics is underpinned by core funding provided by the CRUK Cancer Therapeutics Unit award, the successful renewal of which was led by Workman (£34.69M, 2011-2016; rated Forefront/Outstanding). Springer secured 3 Wellcome Trust Seeding Drug Discovery Awards (£8M).

Bliss led the renewal of the CRUK funding for the Clinical Trials and Statistics Unit (£5M, 2008-2013; £5.84M, 2013-2018; rated Outstanding). Core funding provided by the CRUK and Department of Health for the Experimental Cancer Research Centre, led by Kaye and de Bono, was also renewed twice, (£2.5M, 2007-2012; £2.5M, 2012-2017; rated Outstanding).

All laboratory space is either new or has been refurbished since 2001 and throughout the period the ICR has made substantial investment in ‘state-of-the-art facilities. External funding has been obtained to expand the research space available to the ICR allowing the recruitment of new groups and the expansion of existing ones. The Centre for Molecular Pathology (cost £17.1 million: capital funding from Department of Health to the NIHR BRC, The Wolfson Foundation and the Royal Marsden Cancer Charity) opened in 2012 and provides facilities for molecular diagnostics, tissue sample storage and processing, in addition to laboratory space for molecular pathology and drug discovery/development teams (de Bono, Garrett, Banerji, Sadanandam, Yuan).

All research groups have access to a range of standard, costs effective genetic analyses

provided by the Genetics Core Facility. Using a 96-capillary 3730xl DNA Analyzer the facility performs Sanger DNA sequencing as well as DNA fragment analysis applications including MLPA and microsatellites. A Sequenom mass array analyser is also available for SNP genotyping, methylation detection and quantitative gene expression analysis. More bespoke applications, such as targeted re-sequencing from sub-microgram DNA amounts and shRNA screen deconvolution, can also be provided. Studies of cancer evolution and drug resistance will be supported by the Tumour Profiling Unit (TPU), which has been established to facilitate the 'horizontal' analysis of patient biopsies from diagnosis throughout treatment. ICR investment of £1.7M has enabled laboratory refurbishment and equipment purchases to support genomic capabilities and development of patient derived xenografts. The Genomics Facility within the TPU is a state-of-the-art facility working under GCLP guidelines to provide Next Generation Sequencing. It currently houses two Illumina HiSeq2500 instruments and acquired the first Ion Proton in Europe from Life Technologies, which is able to sequence two whole exomes in as little as 4 hours. The Tumour Transplantation Facility (TTF) within the TPU was set up to generate, archive and analyse patient derived xenografts (PDXs).These animals will be housed in The Biological Services Unit, which has had investment of £1.9M over the assessment period to upgrade facilities.

Over £1.35M of CRUK funding has been secured to fund equipment for drug discovery and development in the CRUK Cancer Therapeutics Unit, including highly sensitive apparatus for biomolecular separation, protein post-translational modification and interaction analysis (ACQUITY UPLC H-Class Bio System, CB1000 protein analysis system, Biacore T100 system The ICR has also spent £500K on upgrading fume hoods for chemistry.

The ICR is investing over £20M to build a Centre for Cancer Imaging (CCI), to provide integrated and expanded facilities for pre-clinical imaging to better enable research to identify non-invasive molecular imaging biomarkers for drug discovery and clinical development. Support for this second phase in the construction of the Sir Richard Doll building has been obtained from the Wolfson Foundation and through ICR fundraising, with the balance funded from SRIF and royalty income. Construction is due to be completed in 2014. The Sutton Biological Services Unit will be re-housed within the CCI. The CCI will capitalise on the significant investment in infrastructure within Radiotherapy and Imaging over the assessment period. A cyclotron facility for production of short lived radionuclides used in radiotherapy treatment has been established. Investment of £6M in the acquisition of 2 new clinical PET/CT machines and refurbishment of space has helped develop the PET/CT Centre with the RM. A pre-clinical PET/CT machine (Skyscan 1076 In-Vivo Micro-CT) has also been procured. There has also been significant investment in MRI, with £3.2m secured from the Wolfson Trust, MRC and Department of Health for the purchase of a 3T MRI machine (Philips Achieva 3.OT TX) and for refurbishment of the space required to house this equipment. Peer-reviewed grant funding of £2.2M has been secured from the EPSRC to pursue High Intensity Focussed Ultrasound for cancer treatment, with a LTE Liver Therapy Unit purchased to help deliver a clinical High Intensity Focussed Ultrasound system.

Key activities at the ICR demand high end computation and large amounts of data storage. Recognising these supercomputing requirements the ICR invested £1.8m to establish a High Performance Computing core facility. The three platforms initially acquired provided a total of 896 usable processors and around 400TB of high performance storage. A further £0.5M has been invested to increase capacity, with three new platforms providing an additional 992 high performance processing cores aligned to 550TB of additional high performance storage. For medical imaging we have established an innovative research picture archiving and communications system (PACS) and integrative framework to enable multifunctional image data analysis in one pipeline. We have employed sophisticated deep machine-learning methodologies to demonstrate automated organ detection from MRI datasets despite disease-induced abnormalities, with important implications for automatic diagnosis, radiotherapy planning, and medical image retrieval.

Benefits-in-kind

The RM/ICR NIHR BRC receives a total of £61,544,000 over 5 years and this funding is awarded to support translational research based in the NHS. The current portfolio included Phase I and II trials, blood/tissue collections, blood/tissue analysis, biomarker identification, diagnostic/prognostic/predictive test development and translational bolt on studies to Phase III trials. Crucially the BRC, together with the ECMC, provide core funding for the Drug Development Unit (DDU). This Phase I clinical facility focuses on biomarker-driven and hypothesis-testing early clinical trials and sees over 500 patients per year for new drug treatment. With over 20 open trials at any one time it is one of the largest such units in the world.

The ICR secured grant funding from the Focused Ultrasound Foundation to establish a Centre of Excellence. Linked to this award, Philips have loaned a Sonalleve High Intensity Focussed Ultrasound system, which is configured as an add-on to the 3T MRI machine installed. Financial support will be provided for participation in a multi-centre Philips sponsored clinical investigation of MR-guided HIFU for the palliation of painful bone metastases. Additionally, a contribution of £100k towards the cost of a PhD studentship at ICR has been offered.

CRUK Centre funding for the CRUK Chair of Paediatric Oncology has been instrumental in securing extension and expansion of the Oak Foundation investment for “Accelerated Drug Development in Children and Young People with Cancer” at the RM. This provides funding for an Oak Consultant in Drug Development and associated trial staff exclusively dedicated to drug development.

Institutional Research Management and Governance

The ICR has an effective governance structure for prioritising research as a core institutional academic activity. Its Board of Trustees oversees scientific strategy and monitors the associated objectives against defined outcome measures. ICR and RM have joint structures for research management and clinical research governance The Joint Research Committee reviews the progress of research programmes that implement the strategy, and advises upon and prioritises new initiatives and their resource implications.

The ICR/RM joint Clinical Research Directorate (CRD), chaired by the Director of Clinical R&D (Professor David Cunningham, also the Director of the NIHR Biomedical Research Centre) with a membership constituted from senior management (including both Chief Executives) and researchers of both institutions, advises Boards of both organisations on all issues and resources relevant to clinical research. All research involving patients, clinical staff, tissues, samples and/or data at ICR and RM (or tissues, samples or data), must be approved by the joint RM/ICR Committee for Clinical Research (CCR) which also provides the mechanism for sponsorship approval. Committee members assigned to review a research proposal include a clinical or scientific peer reviewer, a statistician, a GCP compliance specialist and a pharmacist under the direction of the CCR Chair. CCR reviews research for scientific quality, research governance arrangements, compliance with the EU Directive, resource implications and insurance arrangements, and conducts a formal risk assessment to ensure that studies are not approved until all scientific and regulatory requirements have been met and that areas of risk to the institution have been identified and addressed. Sponsorship arrangements are assessed on a case by case basis by the CCR.

The Clinical R&D Office, located at RM and under the direction of the Director of Clinical Research, is the sponsor office for both the ICR and RM and is responsible for servicing the joint RM/ICR CCR; for developing and managing RM/ICR systems for good governance and management of clinical research; facilitating inspections carried out by the regulatory authorities; providing Good Clinical Practice and pharmacovigilance training to RM/ICR clinical research personnel; and for providing support for monitoring and auditing of clinical research.

e. Collaboration or contribution to the discipline or research base

De Bono (2012), Cunningham (2011), Dowsett (2013), Eeles (2012) and Houlston (2010) were

elected as **Fellows of The Academy of Medical Sciences** to bring the total number of FMedSci submitted to UoA1 to 10 (Horwich, Kaye, Leach, Swerdlow, Workman).
NIHR Senior Investigators: Horwich (2008), Eeles (2008, 2011), Yarnold (2008, 2011), Dearnaley (2008, 2012), Leach (2008, 2013), Dowsett (2009, 2013), Kaye (2009), Brown (2008), Cunningham (2008), Gore (2008), Swerdlow (2008).

Prizes:
AACR Team Science Award – Workman, Al-Lazikani, Banerji, Blagg, Collins, de Bono, Eccles, Garrett, Hoelder, Jones, Kaye, Linardopoulos, Marais, Raynaud, Springer, van Montfort - the first non-US based team to win the AACR Team Science Award.
CRUK Translational Research Prize 2013 – Workman, Clarke, Eccles, Banerji, Collins, Jones
McElwain Prize (Banerjee, 2009), Sylvia Lawler Prize (Blackledge, 2013), Hubertus Wald Prize (Cunningham, 2009), Association of Cancer Physicians McElwain Prize (Yap, 2012).

Other senior awards: Dowsett Jean H Lubrano Lecture, 2008; Elizabeth Hurley Research Award 2010, Luigi Castagnetta Memorial Award, 2012; **Horwich** Royal College of Surgeons of Ireland FFR RCSI (Hon) 2009; **Kaye** BACR/NCRI Award Lecture 2010; **Leach** British Journal of Radiology Barclay Medal, 2009; British Journal of Radiology Silvanus Thompson Lecture and Medal 2010; **Nutting** Mackenzie Davidson Memorial Medal and Lecture 2010; **Smith** Susan J Komen for the Cure (2009); Brinker Award for Scientific Division 2009, **Ter Haar** International Society for Therapeutic Ultrasound Francis & William Fry Award for Lifetime Achievement, 2012; ESHO BSD Award 2012, Society of Thermal Medicine George Hahn Award, 2013, British Medical Ultrasound Society Donald MacVicar Brown Lecture, 2012; **Workman** BACR/NCRI Tom Connors Award Lecturer 2009, Royal Society of Chemistry George & Christine Sosnovsky Award 2010, New Zealand Society for Oncology Bruce Cain Memorial Lecturer 2012, Royal Society of Chemistry Chemistry World Entrepreneur of the Year 2012; **Yarnold** European Breast Cancer Congress Emmanuel van de Scheuren Memorial Lecture 2010.

Fellowships:
Wellcome Trust Senior Investigator Award (Müschen, 2013), CRUK Senior Fellowship (Davies, 2011), CRUK Clinician Scientist Fellowship (Attard); Netherlands Organisation for Scientific Research, Rubicon grant (Aarts, 2011), NIHR Academic Clinical Lecturer (Attard, Hewish, Yap 2013), NIHR Postdoctoral Research Fellowship (Blackledge, 2012).

Faculty have been members of at least 113 committees in the period, 25 have held chairs/vice chairs/group leaders/president/vice presidents including:
Bamber Chair, Scientific and Education Committee at the British Medical Ultrasound Society; **Eccles** Chair, Scientific Advisory Committee at Breast Cancer Campaign; **Flux** Chair, Molecular Radiotherapy sub-committee of Radiotherapy Committee, British Institute of Radiology; **Gore** Chair, UK Gene Therapy Advisory Committee; **Leach** Chair, British Chapter at the International Society of Magnetic Resonance in Medicine; **Robinson** Group Leader, Imaging, Detection and Screening Gap Analysis at Breast Cancer Campaign; **Shaw** Chair, WMDA Clinical Working Group, World Marrow Donor Association; Donor Health and Safety Working Committee at CIBMTR; **Swerdlow** Chair, Standing Committee on Epidemiology (ICNIRP) at the International Commission.

41 members of Faculty are on editorial boards.

Partnership and collaboration - Transforming outcomes for patients
Within the ICR's research strategy, key strategic objectives are:

- To form strategic alliances and collaborations which enhance opportunities to conduct research aimed at improving outcomes for cancer patients
- To ensure appropriate and effective exploitation of the ICR's intellectual property and research outputs to maximise patient benefit

At the core, the ICR will continue its partnership with RM and ensure we have the most appropriate research and governance structures in place to translate our findings in basic

research to the clinical setting. However we will also forge broader alliances and collaborations where these will enhance our research. We have jointly established a Centre for Systems Oncology and Cancer Innovation with Imperial College. The physicists will collaborate with UCL to develop the use of proton beam therapy. Our partnership with RM has been extended to include an academic and research partnership with Mount Vernon Hospital. We have established The London Lung Cancer Alliance which aims to deliver dramatic benefits for patients through collaboration, coordination and an ambition to give every patient access to a trial suitable for them. The Alliance is: ICR, RM, IC and Imperial College Healthcare NHS Trust, King's College London (as part of King's Health Partners Academic Health Sciences Centre), Royal Brompton & Harefield NHS Foundation Trust, St George's Healthcare NHS Trust and Barts Cancer Institute at Queen Mary. The London Lung Cancer Alliance will also link up with five other cities across the UK: Newcastle, Southampton, Liverpool, Cardiff and Edinburgh.

The **National Cancer Research Institute (NCRI)** is a UK-wide partnership between government health departments, charities, research councils and industry, which exists to promote communication, coordination and collaboration in cancer research. ICR/RM Faculty are involved in 14 NCRI Clinical Studies Groups: Biomarkers and Imaging, Bladder Cancer, Breast Cancer, Children's Cancer and Leukaemia, Colorectal Cancer Group, Gynaecological Cancer, Haematological Oncology, Head and Neck Cancer, Lymphoma, Melanoma, Prostate Cancer, Renal Cancer, Testis Cancer and Upper Gastro-Intestinal. ICR/RM Faculty Chair the following Clinical Studies Groups: Biomarkers and Imaging Clinical Studies Group (Brown), Renal Cancer (Larkin), Novel Agents Subgroup of the Children's Cancer and Leukaemia Clinical Studies group (Pearson), Myeloma Subgroup in the Haematological Oncology Clinical Studies Group (Davies), Systematic Therapy and Radiotherapy Subgroup in the Head and Neck Cancer Clinical Studies Group (Harrington), Oesophagogastric Subgroup of the Upper Gastro-Intestinal Clinical Studies Group (Cunningham).

Our primary objective for the ICR's discoveries is that they are developed first and foremost for patient benefit. In addition, we seek to achieve a fair financial return as an outcome for any exploitation by commercial organisations of ICR discoveries. If a discovery such as a diagnostic or bio-marker can be used widely with little or no further development, it is made available freely or through non-exclusive licensing; exclusive licensing is limited to those discoveries, primarily new therapeutics, which require substantial further investment from an industrial partner to realise patient benefit.

The CRUK Cancer Therapeutics Unit takes the lead on several Phase I trials sponsored by the CRUK New Agents Committee and has particularly close links in drug development studies with Imperial College London, NICR at Newcastle University and Beatson Institute at Glasgow University. Workman chairs the CRUK PK/PD Technology Advisory Committee. The Paediatrics Group within the Division of Clinical Studies is one of four UK centres selected for CRUK/DOH support to conduct Phase I trials. The CRUK funded ICR Clinical Trials and Statistics Unit (ICR-CTSU) is one of seven CRUK core-funded cancer clinical trials units. It is a key resource for several NCRI trials groups (breast, urology, head & neck and others) and also collaborates internationally.

International collaborations play a vital role in both early clinical trials and in late phase randomised trials. Similarly, genetics and epidemiology have strong national and international collaborations which underpin large-scale studies. During the assessment period, ICR/RM international collaboration has increased in both volume terms and in relative terms as a percentage of our research output, as evidenced by internationally co-authored publications. In descending order, our most frequent collaborating partners are from the USA, Germany, France, the Netherlands and Italy.