Institution: The Institute of Cancer Research

Unit of Assessment: UoA1

Title of case study: Identifying genes that increase the risk of developing cancer and exploiting these discoveries to enhance patient care and improve public health.

1. Summary of the impact

The ICR has a world-leading role in identifying, characterising and clinically exploiting genetic factors that predispose to cancer. This has had a direct and significant impact on public health and patient care; over 250,000 clinical tests for gene modifications that were identified at ICR are performed annually worldwide. Many thousands of families have benefited through optimised treatments for individuals with cancer and improved cancer risk estimation, targeted screening and risk-reducing measures for their relatives. Cancer genes discovered at the ICR include breast cancer genes (*BRCA2*, *CHEK2*, *BRIP1*, *PALB2*), ovarian cancer genes, (*BRCA2*, *RAD51D*, *PPM1D*), a renal cancer gene (*FH*) and childhood cancer genes (*BUB1B*, *PALB2*, *EZH2*).

2. Underpinning research

In 1994, a team led by Professor Mike Stratton and Professor Richard Wooster (both ICR Faculty) mapped a familial breast cancer gene to chromosome 13q, and a year later, together with Professor Alan Ashworth (ICR Faculty), they isolated *BRCA2* (Ref 1). *BRCA2* mutations confer increased risks of breast and ovarian cancer; this discovery has transformed the clinical management of familial breast cancer. Moreover, a better understanding of the biological consequences has led to improved treatment for patients with familial breast and ovarian cancer. The ICR scientists were the first to publish the identification of *BRCA2* and show that cells lacking BRCA1 or BRCA2 are highly sensitive to drugs inhibiting poly-ADP-ribose polymerase (PARP), providing a ground-breaking therapeutic approach.

Discovery of the *BRCA* mutations has led to changes in the way women with this high genetic risk of breast cancer are monitored by mammographic imaging. The research underpinning this advance was led by Professor Martin Leach (ICR Faculty) in the MARIBS clinical trial, which demonstrated that screening by magnetic resonance imaging (MRI) was considerably more sensitive than X-ray mammography (Ref 2).

In 2001, Professor Nazneen Rahman (ICR Faculty), together with Stratton, embarked on an innovative strategy to identify DNA repair genes that predispose to breast cancer. Mutational screening of the entire coding sequence of candidate genes was undertaken; large numbers of cases and controls were used to provide robust and meaningful comparison of the number of pathogenic mutations between the two groups. This work resulted in the identification of mutations in *CHEK2* (2002), *BRIP1* (2006) and *PALB2* (2007; Ref 3) and provided genetic evidence of the association of *ATM* mutations and breast cancer, resolving 20 years of controversy. This research was underpinned and guided by epidemiological data from a national familial breast cancer study, initiated by Rahman in 2001, that is now the largest series in the world, including over 10,000 families (www.icr.ac.uk/bocs; http://public.ukcrn.org.uk/Search/StudyDetail.aspx?StudyID=6542). In 2011, Rahman and Dr Clare Turnbull (ICR Faculty) extended this epidemiological study to ovarian cancer and identified that *RAD51D* and *RAD51C* gene mutations confer substantial increases in risk of the disease (Ref 4).

From 2005 onwards, Rahman also led a successful team in childhood cancer predisposition gene discovery, and has recruited one of the largest series of families with childhood cancer in the world. The research has identified several genetic and epigenetic factors that predispose to various childhood cancer syndromes, including *BUB1B* (Ref 5), *PALB2*, epigenetic defects on chromosome 11 at 11p15 (Ref 6), *EZH2* and *CEP57*. These genetic factors predispose the carriers to diverse childhood cancers and associated syndromes.

In 2002, Professor Richard Houlston (ICR Faculty) was one of the lead investigators in the international collaboration that discovered that mutations in the FH gene cause Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC) syndrome (Ref 7).

From 2006, a team led by Dr Gareth Morgan and Dr Faith Davies (both ICR Faculty) has characterised the molecular pathogenesis of multiple myeloma (MM) with the aim of defining new therapeutic targets and personalising treatment strategies. This research has provided biologically relevant prognostic/predictive factors that have been integrated into standard risk stratification approaches. Examples include: the t(1:14) and MAF translocations, shown to be associated with impaired survival; and the loss of heterozygosity at 16q that identified *WWOX* and *CYLD* as tumour suppressor genes. Furthermore, the role of inherited variation in MM has also been defined with 6 common loci being identified, as well as the mechanism leading to the initiation of MM by translocation into the Ig gene loci. The common variants mediating myeloma risk were identified, including at 3p22.1 and 7p15.3, and these cytogenic markers are now being used for patient prognosis.

3. References to the research

All ICR authors are in bold and ICR team leaders/Faculty are in bold and underlined.

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6. **Scott RH, Douglas J, Baskcomb L**, Nygren AO, Birch JM, Cole TR, Cormier-Daire V, Eastwood DM, Garcia-Minaur S, Lupunzina P, Tatton-Brown K, Bliek J, Maher ER, **Rahman N**. 2008, Methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA) robustly detects and distinguishes 11p15 abnormalities associated with overgrowth and growth retardation, J Med Genet. 45 (2), 106-113. (http://dx.doi.org/10.1136/jmg.2007.053207)

7. The Multiple Leiomyoma Consortium: Group 1: Tomlinson IP*, Alam NA, Rowan AJ, Barclay E, Jaeger EE, Kelsell D, Leigh I, Gorman P, Lamlum H, Rahman S, Roylance RR, Olpin S, **Group 2: Bevan S, Barker K, Hearle N, Houlston RS*,** Group 3: Kiuru M, Lehtonen R, Karhu A, Vilkki S, Laiho P, Eklund C, Vierimaa O, Aittomäki K, Hietala M, Sistonen P, Paetau A, Salovaara R, Herva R, Launonen V, Aaltonen LA*; Multiple Leiomyoma Consortium. 2002,

Germline mutations in *FH* predispose to dominantly inherited uterine fibroids, skin leiomyomata and papillary renal cell cancer, Nat Genet. 30 (4), 406-410. (http://dx.doi.org/10.1038/ng849)

Selected research grant support

1. Rahman – Era of Hope Scholar Award: "Identification, characterisation and clinical development of the new generations of breast cancer susceptibility alleles", USAMRMC, 2005-2011, $3,1M
2. Houlston – "Molecular and population studies of inherited cancer susceptibility" Cancer Research UK, 2007-2012, £2.8M
3. Leach – "The UK study of MRI screening for Breast Cancer", Medical Research Council, 2002-2005, £890k

4. Details of the impact

The ICR research identifying numerous genetic factors that predispose to cancer underpins significant impact on multiple and diverse aspects of patient care and treatment, and on the public health of unaffected individuals.

For affected patients, genetic testing for cancer predisposition genes is key to the precise diagnosis of the disease; it also guides the subsequent treatment and management of the patient, with significant benefits to their care, wellbeing and treatment outcomes. Genetic testing also provides guidance to relatives by identifying at-risk, but unaffected, individuals for screening or risk-reducing interventions. The identification of genetic factors may also provide clues as to the origins of a patient's cancer and alleviate their often distressing concerns over the causes of the disease.

Predisposition genes discovered at the ICR have led to direct clinical impact for patients and are currently part of routine clinical management of various cancers. For example, the ICR discovery that *BRCA2* mutations conferred increased risks of breast and ovarian cancer led directly to a NICE clinical guideline (CG41) [1]. Building on this work, the MARIBS clinical trials, led by Leach's team at ICR, addressed the role of MRI screening of women who are *BRCA* mutation carriers and at increased risk of disease (Research Ref 2 above). The study demonstrated that MRI screening was significantly more sensitive than X-ray mammography in this group of younger women and has resulted in new NICE guidance (NICE clinical guideline CG41, replaced by CG164 in June 2013 [2]). MRI screening for such women is now standard care in the UK. Since this group of women at higher risk of cancer are more regularly screened, the use of MRI rather than X-ray exposure has had an additional impact on improving the safety of screening procedures and the wellbeing of the women being screened. The outcomes of the MARIBS study also resulted in American Cancer Society recommendations for MRI screening for early breast cancer detection in women without overt symptoms [3].

Mutations in *BUB1B* and *CEP57* cause a condition known as mosaic variegated syndrome (MVA). This syndrome has a high risk of childhood mortality, primarily because of a very high risk of childhood cancer. MVA is an autosomal recessive condition and the identification of two of the underlying genes at the ICR has led to both diagnostic and prenatal testing becoming available. Importantly, the risk of cancer is primarily the result of *BUB1B*-related MVA, and the prognosis for non-*BUB1B* cases is substantially improved, which is a significant benefit to affected families. Gene testing for MVA has not yet been made available in NHS laboratories. However, since 2008, the ICR has increasingly received requests from clinicians both in the UK and in other countries to undertake such testing, and between 2008 and 2013, 147 individuals (in 54 families) have been tested for MVA-related genetic mutations.

The ICR discovered that *PALB2* mutations predispose to childhood cancer and a condition known as Fanconi Anaemia, if two mutations are present, acting in an autosomal recessive fashion; they also predispose to breast and other cancers in adults carrying one mutation, acting in an autosomal dominant fashion. Testing for *PALB2* mutations is currently a routine part of genetic testing available in the NHS [4]. Guidelines regarding Fanconi Anaemia, including the role of

PALB2, are outlined in the Fanconi Anaemia section of the gold standard international clinical reviews, NCBI GeneReviews™ [5].

For the *EZH2* and *NSD1* genes, which cause childhood-overgrowth clinical conditions, ICR's research has demonstrated that the majority of mutations arise for the first time in the affected child (*de novo* mutations), and hence the risk to siblings of children with these mutations is extremely low. The impact and value of this type of information for parents cannot be over-estimated and tests for these genes are currently performed in the NHS (EZH2 [6] and NSD [7]). The NCBI GeneReviews™ for these genes were written by Rahman together with her colleagues (*EZH2* [8] and *NSD1* Review [9]).

For *RAD51D, RAD51C* and *FH*, genetic testing is currently undertaken in familial ovarian cancer, and HLRCC families [10]; on this basis screening and preventative strategies are offered to mutation carriers.

Genetic research at the ICR has also contributed to the methodological implementation of gene discoveries into clinical practice. For example, the demonstration that epigenetic defects at 11p15 result in childhood cancer and childhood growth disorders. Detecting epigenetic abnormalities is technically challenging, particularly in a clinical diagnostic setting. The ICR optimised a technique called MS-MLPA and undertook extensive evaluation and validation in clinical samples, partnering with NHS diagnostic laboratories (for example St George's and Great Ormond Street) so that the test would be available to affected families through the NHS. Since 2008, MS-MLPA has replaced the previous methods that had been used and it is employed as the standard technique in the UK and other European countries (See Beckwith-Wiedemann Syndrome entry on NCBI Gene Reviews™ [11]).

Research at the ICR has also demonstrated the benefits of using genetic testing for selecting which patients are likely to respond to specific therapies. For example, work at ICR showed that patients with *BRCA1* and *BRCA2* mutations are likely to respond to treatment with PARP inhibitors. From research on understanding the molecular genetics of MM, tumour translocations and mutations are now being used as prognostic markers to stratify treatment and as predictive markers to assess responses to specific therapies with corresponding patient benefit.

The research at the ICR on identification of cancer predisposition genes has also had significant commercial impact. In 2011, the ICR partnered with Illumina – the market leader in next-generation sequencing technologies – to develop a single test, known as TruSight Cancer panel. This is designed to enable the analysis of genes and genetic variants associated with predisposition to cancer for less than the cost of a single gene test by standard technology. This test is currently being marketed by Illumina [12].

5. Sources to corroborate the impact

[1] NICE Guideline CG41 – http://www.nice.org.uk/nicemedia/pdf/cg41niceguidance.pdf
[2] NICE Guideline CG164 – http://publications.nice.org.uk/familial-breast-cancer-cg164
[3] American Cancer Society recommendations, 7th Feb 2013 – http://www.cancer.org/acs/groups/cid/documents/webcontent/003178-pdf.pdf
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