Institution: The Institute of Cancer Research

Unit of Assessment: UoA5

Title of case study: BRCA genes in cancer; improved screening regimes and novel therapies.

1. Summary of the impact

Scientists at The Institute of Cancer Research (ICR) have identified a breast cancer susceptibility gene, *BRCA*2, and advanced the understanding of the function of the *BRCA* genes. Following the discovery and cloning of *BRCA2,* further research demonstrated that *BRCA* mutations are also associated with ovarian, prostate and pancreatic cancers. *BRCA* testing is now routinely used by health services worldwide to identify those at high risk of developing cancer and advise them on preventative strategies. ICR research showed that magnetic resonance imaging (MRI) was more sensitive than X-ray mammography when screening for tumours in *BRCA* carriers, and this is now the standard of care in the UK. Through further research on *BRCA* function, ICR scientists demonstrated that PARP inhibitors were effective in treating breast cancer in mutant *BRCA* carriers. This has led to the rapid development of poly-ADP-ribose polymerase (PARP) inhibitors as drugs for targeted use against breast and ovarian cancers with a *BRCA* mutation as well as a recent submission to regulatory authorities for approval and registration in Europe for the use of the PARP inhibitor olaparib for maintenance treatment of *BRCA* mutated ovarian cancer.

2. Underpinning research

The clinical observation that breast cancer runs in some families led scientists to search for the genetic basis of such familial predisposition. In 1995, an ICR team led by Professor Michael Stratton (ICR Faculty) and Dr Richard Wooster (ICR postdoctoral researcher, 1991-1996, and ICR Faculty, 1997-2002) mapped the location of the second breast cancer susceptibility gene, *BRCA2,* to chromosome 13q, and then together with Professor Alan Ashworth (ICR Faculty) they isolated the *BRCA2* gene (Ref 1). The ICR team were the first group to publish this finding.

BRCA2 mutations confer increased risk of breast and ovarian cancer in women, men have an increased risk of developing early onset prostate cancer, and both men and women are at increased risk of pancreatic cancer. The discovery of *BRCA2* and its association with specific cancers paved the way for the introduction of genetic testing and enhanced screening programmes for those at risk, and is also leading to the development of new anti-cancer drugs.

Subsequent research on the function of the protein encoded by the *BRCA2* gene by the Ashworth team at ICR demonstrated its key role in DNA repair (Ref 2) and further demonstrated precisely how wildtype BRCA2 and mutated BRCA2 function in this cellular process (Ref 3). From these studies, the Ashworth team proposed that cells lacking either BRCA1 or BRCA2 function would be highly sensitive to drugs that inhibit PARP, an enzyme which plays a key role in an alternative DNA repair pathway, and went on to confirm this experimentally (Ref 4). These observations had an immediate impact, leading rapidly to clinical trials, the first of which was carried out by ICR investigators (Ref 5) with olaparib (AZD2281), a novel, potent, orally active PARP inhibitor which has demonstrated remarkable clinical effectiveness in breast, ovarian and prostate cancer patients carrying mutant forms of *BRCA1* or *BRCA2.*

The use of a PARP inhibitor for cancers with *BRCA* mutations was the first demonstration of the successful use of a synthetic lethality strategy in the clinic. Synthetic lethality arises when inhibition of two genes/proteins leads to cell death, whereas inhibition of only one does not. Inhibition can be due to mutation or administration of an inhibitor.

Anticipating a potential mechanism of resistance, the Ashworth team discovered a completely novel process whereby deletions occur within the *BRCA2* gene, restoring some functionality and leading to drug resistance (Ref 6).

3. References to the research

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

1. **Wooster R, Bignell G**, Lancaster J, **Swift S, Seal S, Mangion J, Collins N**, Gregory S, Gumbs C, Micklem G., **Barfoot R**, **Hamoudi R**, **Patel S**, Rices C, **Biggs P**, **Hashim Y**, **Smith A**, **Connor F**, Arason A, Gudmundsson J, Ficenec D, Kelsell D, **Ford D**, Tonin P, Bishop DT, Spurr NK, Ponder BAJ, **Eeles R**, **Peto J**, Devilee P, Cornelisse C, Lynch H, Narod S, Lenoir G, Egilsson V, Barkadottir RB, Easton DF, Bentley DR, Futreal PA, **Ashworth A** & **Stratton MR.** 1995, Identification of the breast cancer susceptibility gene BRCA2, Nature. 378, 789-792. (http://dx.doi.org/10.1038/378789a0)
2. **Connor F**, **Bertwistle D**, Mee PJ, **Ross GM**, **Swift S**, Grigorieva E, Tybulewicz VL, & **Ashworth A.** 1997, Tumorigenesis and a DNA repair defect in mice with a truncating Brca2 mutation, Nature Genetics. 17, 423-430. (http://dx.doi.org/10.1038/ng1297-423)
3. **Tutt A**, **Bertwistle D**, **Valentine J**, **Gabriel A**, **Swift S**, **Ross G**, Griffin C, Thacker, J & **Ashworth A.** 2001, Mutation in Brca2 stimulates error-prone homology-directed repair of DNA double-strand breaks occurring between repeated sequences, EMBO J. 20, 4704-4716. (http://dx.doi.org/10.1093/emboj/20.17.4704)
4. **Farmer H**, **McCabe N**, **Lord CJ**, **Tutt AN**, **Johnson DA**, **Richardson TB**, **Santarosa M**, Dillon KJ, Hickson I, Knights C, Martin NM, Jackson SP, Smith GC & **Ashworth A.** 2005, Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy, Nature. 434, 917-921. (http://dx.doi.org/10.1038/nature03445)
5. **Fong PC**, Boss DS, Yap TA, **Tutt AN**, **Wu P**, Mergui-Roelvink M, Mortimer P, Swaisland H, Lau A, O'Connor MJ, **Ashworth A**, Carmichael J, **Kaye SB**, Schellens JH, **de Bono JS**. 2009, Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers, N Engl J Med. 361 (2), 123-134. (http://dx.doi.org/10.1056/NEJMoa0900212)
6. **Edwards SL, Brough R**, **Lord CJ**, **Natrajan R**, **Vatcheva R**, Levine DA, Boyd J, **Reis-Filho JS**, **Ashworth A**. 2008, Resistance to therapy caused by intragenic deletion in BRCA2, Nature. 451, 1111-1116. (http://dx.doi.org/10.1038/nature06548)

Selected research grant support

1. Stratton – "Isolation of the *BRCA2* gene", 1995-1998, Cancer Research Campaign, £221,244.
2. Ashworth – "*BRCA1* and *BRCA2* genes and gene products", 1997-2000, Breakthrough Breast Cancer, £350,000, programme grant renewed in 2004 and 2009.
3. Leach / Eeles – "National multicentre study of magnetic resonance imaging (MRI) as a method of screening in women at genetic risk of breast cancer", 1997 - 2002, extended 2002 – 2005, Medical Research Council and NHS Executive, £ 4,447,753.

4. Details of the impact

The work of ICR scientists on the *BRCA* genes has had a major clinical impact and has resulted in significant improvements in care for those with *BRCA* mutations, as well as having the commercial impact of stimulating the development of new drugs by pharmaceutical companies. These impacts stemmed from the identification of the *BRCA2* gene in 1995 (Research Ref 1 above). 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.

The ICR, with its clinical partner the Royal Marsden NHS Foundation Trust (RM), has prepared

genetic testing protocols to facilitate implementation of *BRCA* testing in mainstream oncology [1]), is coordinating an audit of the new protocols which will inform national guideline,s and has provided resources for *BRCA2* patients ("A beginners guide to BRCA1 and BRCA2" [2]). This guide is regularly downloaded (for example, 316 downloads in the period 15 May to 24 July 2013). The ICR/RM clinical teams run regular patient update days for *BRCA* carriers and (in collaboration with Macmillan) have produced a patient information booklet for carriers; "Cancer genetics – how cancer sometimes runs in families" [3]. ICR/RM have also developed a Carrier Clinic model for the management of *BRCA* carriers, which has been widely adopted [4]. *BRCA2* testing is now routinely used by health services worldwide to identify those at high risk of developing cancer and to advise on preventative strategies (NICE clinical guideline CG41 [5]; US Preventative Services Task Force). It is estimated that in the US alone over 100,000 individuals are screened per year (Myriad.com web site). NICE estimate that currently in the UK 7 per 100,000 population are undergoing testing and that this number is likely to treble in the next few years.

Following on from the discovery of the *BRCA1 and BRCA2* genes and the recognition of their role in conferring predisposition to breast cancer, a team led by Professors Martin Leach and Ros Eeles (ICR Faculty, UoA1) carried out a national multicentre study, the MARIBS clinical trial, looking at the role of magnetic resonance imaging (MRI) in women who are *BRCA* mutation carriers [6]. The study demonstrated that in this group of women, screening for tumours by MRI was significantly more sensitive than X-ray mammography. The results of the MARIBS clinical trial formed the foundation of new NICE guidance (NICE clinical guideline CG41, replaced in June 2013 by CG164 [7]). MRI screening for such women is now standard care in the UK, and since this group of women at higher risk of cancer is more regularly screened and from an earlier age, the use of MRI rather than X-ray exposure has had an additional major benefit of improving screening safety. The outcomes of the MARIBS study also resulted in American Cancer Society recommendations for MRI screening for early breast cancer detection in high risk women without breast symptoms [8].

Research by Ashworth's team at the ICR has demonstrated the critical role of BRCA2 in DNA repair and later the synthetic lethal effect of PARP inhibitors in *BRCA1* and *BRCA2* mutated tumours (Research Ref 3 above). These research findings rapidly led to clinical trials of olaparib (AZD2281), a novel, potent, orally active PARP inhibitor, and in July 2009, the Phase I results were published, showing remarkable clinical impact in breast, ovarian and prostate cancer patients carrying mutated forms of *BRCA1* or *BRCA2* [9]. Olaparib was initially developed by the UK company KuDOS (later acquired by AstraZeneca) as a potential chemo- and radiotherapy sensitiser. ICR work showed how this drug could be used to most effect in *BRCA* carriers, leading AstraZeneca to invest in further research. Olaparib has now been tested in multiple clinical trials worldwide involving over 3,000 patients (ClinicalTrials.gov; for example trial NCT00753545, conducted at RM) and is moving into Phase III studies (Nature News 11 Sep 2013). A number of other companies are developing PARP inhibitors as a direct result of the insight provided by the research at ICR (for example, Clovis – NCT01009190, Biomarin – NCT01286987, Eisai – NCT01618136, Abbott – NCT01051596; see ClinicalTrials.gov).

The research by ICR in this field has had a major impact on patient treatment and outcome. In particular, the presence of a *BRCA* mutation in ovarian cancer patients is predictive of a good response to treatments such as carboplatin and PARP inhibitors. It is now becoming common for HGS (high grade serious) ovarian cancer patients to be tested for *BRCA* mutations to guide treatment choices. ICR and RM, under the leadership of Professor Stan Kaye (ICR Faculty), led an international and multi-centre Phase II study of olaparib in BRCA mutated ovarian cancer which confirmed the high level activity of this type of drug and established the likely importance of dose, recommending monotherapy with olaparib 400 mg twice per day as a suitable dose to explore in further studies (Research Ref 5 above). This encouraged investigators and AstraZeneca to focus on this particular subgroup of patients, and on the basis of a positive outcome from a further randomised trial, olaparib has been put forward to the regulatory authorities for approval and registration in Europe for the maintenance treatment of *BRCA* mutated ovarian cancer.

5. **Sources to corroborate the impact**

[1] www.icr.ac.uk/protocols, protocol 2

[2] "A beginners guide to BRCA1 and BRCA2" http://www.royalmarsden.nhs.uk/consultants-teams-wards/clinical-units/cancer-genetics-unit/pages/brca-booklet.aspx

[3] "Cancer genetics - how cancer sometimes runs in families", MAC11673, Edition 4 – 2012

[4] Bancroft EK et al. 2010, The carrier clinic: an evaluation of a novel clinic dedicated to the follow-up of BRCA1 and BRCA2carriers—implications for oncogenetics practice. J Med Genet, 47, 486-497 (http://dx.doi.org/10.1136/jmg.2009.072728)

[5] NICE Guideline CG41 (http://www.nice.org.uk/nicemedia/pdf/cg41niceguidance.pdf)

[6] Leach MO et al. 2005, Lancet. 365, 1769-78. (http://dx.doi.org/10.1016/S0140-6736(05)66481-1)

[7] NICE Guideline CG164 (http://publications.nice.org.uk/familial-breast-cancer-cg164)

[8] American Cancer Society recommendations, 7th Feb 2013

(http://www.cancer.org/acs/groups/cid/documents/webcontent/003178-pdf.pdf)

[9] Kaye SB et al. 2012, Phase II, open-label, randomized, multicenter study comparing the efficacy and safety of olaparib, a poly (ADP-ribose) polymerase inhibitor, and pegylated liposomal doxorubicin in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer. J Clin Oncol. 30(4): 372-9 (http://dx.doi.org/10.1200/JCO.2011.36.9215)