Institution: University of Sheffield

Unit of Assessment: 3C - Allied Health Professions: Biomedical science

Title of case study: Development of a new clinical intervention enabling personalised breast cancer treatment

1. Summary of the impact

Researchers at the University of Sheffield developed a novel tailored therapy for some forms of breast cancer. This was the first example of the *selective* killing of a tumour using an inhibitor of a DNA repair enzyme (PARP) to induce synthetic lethality, heralding an era of personalised cancer therapy. The discovery was patent protected and development rights sold to Astra-Zeneca who undertook successful phase I and II clinical trials. Disclosure of the findings stimulated intense investment in research and development and has revolutionised approaches to cancer therapy. There are now eight PARP inhibitors in phase I to III clinical trials (92 currently listed involving several leading pharmaceutical companies and thousands of patients) targeting a wide range of tumour types.

2. Underpinning research

Researchers in the Institute for Cancer Studies at the University of Sheffield, led by Dr Thomas Helleday (1999-2007) and Dr Helen Bryant (2002-present), discovered in 2005 [**R1**] that cells deficient in the tumour suppressor gene BRCA2 become acutely sensitive and die in the presence of inhibitors of the DNA repair enzyme poly(ADP-ribose) polymerase (PARP). Based on this discovery they proposed that cancer cells depend on two DNA repair pathways to progress through the cell cycle and maintain viability. The first pathway, single-strand break repair, corrects DNA breaks that occur as a result of intracellular and extracellular environmental stresses that cause DNA damage and depends upon PARP function. The second pathway utilises a BRCA2-dependent DNA repair pathway called homologous recombination (HR) to repair any double strand breaks generated when DNA replication encounters unrepaired single-strand breaks. Cancer cells can cope with loss of a single pathway but not both. As a result, if PARP is inhibited in BRCA2 deficient cancer cells the cells die by apoptosis ("synthetic lethality").

Helleday and his team developed a therapeutic application stemming from this discovery where tumours of individuals inheriting BRCA2 mutations would be acutely sensitive to PARP inhibitors while normal cells would be unaffected. This was first demonstrated by Helleday in collaboration with Nicola Curtin at Newcastle University in the 2005 publication [**R1**]. Using a mouse model system they showed that BRCA2-deficient tumour cell growth was strongly suppressed by a PARP inhibitor while cells containing a functional BRCA2 gene were not affected. This proved to be the first demonstration of the efficacy of a targeted therapy in a synthetic lethality context, opening the door to tailored therapies for cancer patients on the basis of genetic screening (*e.g.* BRCA2 status).

As a result of these findings Helleday filed a patent application in July 2004 (23/07/04) for the use of PARP inhibitors as a targeted therapy for tumours occurring in individuals carrying BRCA2 mutations. Patent WO/2005/012524 was granted to in 2005 [**R2**], the same year that details of the first report of this novel therapy were published in *Nature* [**R1**]. In January 2007 Helleday moved to Oxford University where he continued this research, while Bryant continues related research at the University of Sheffield.

In 2005 patent WO/2005/012524 was licensed to KUDOS therapeutics who initiated phase I clinical trials with an oral PARP inhibitor KU59436 (olaparib), and subsequently AstraZeneca who acquired KuDOS in 2006 on the basis of its strong DNA repair product platform and initiated phase I/II trials with the PARP inhibitor olaparib. These trials, reported in 2009/10, proved highly successful and provided proof of concept of the tolerability and efficacy of a PARP inhibitor in the treatment of tumours in patients inheriting BRCA2 or BRCA1 mutations.

3. References to the research

R1. **Bryant, H.E**.; Schultz, N.; **Flower, D.; Lopez, E.**; Kyle, S.; **Meuth, M.**; Curtin, N.J.; **Helleday, T.** (2005) Specific killing of BRCA2 deficient cells by inhibitors of poly(ADP-ribose) polymerase. *Nature* 434: 913-17. doi: 10.1038/nature03443

R2. Patent: WO/2005/012524. Use of RNAi inhibiting PARP activity for the manufacture of a medicament for the treatment of cancer, The University of Sheffield and **Thomas Helleday** applicants. Publication date, 10.02.2005

4. Details of the impact

Helleday's breakthrough has impacted on economic activity in the healthcare sector, energising PARP inhibitor research and trials and stimulating the search for more specific targets in cancer and other disease states. The proof-of-concept of the synthetic lethality approach has improved the prospects for cancer patients.

As a result of this research **survival outcomes for a large number of cancer patients have improved**. The phase I study at the Royal Marsden National Health Service Foundation Trust and the Netherlands Cancer Institute (KuDOS/AstraZeneca) was published in 2009 and presented at the American Society for Clinical Oncology annual meeting in 2009. The impact of these studies on the field of clinical oncology was immediately apparent and the studies were acknowledged for being the first report of an agent for targeted therapy that improved survival in patients and the first time a survival benefit was obtained in a randomised phase II clinical trial [**S1**].

The initial phase I trial assessed the effects of the PARP inhibitor in 60 patients with a range of solid tumours refractory to conventional therapies including 22 known to carry BRCA1 or BRCA2 mutations. This trial showed that the PARP inhibitor (olaparib) administered as a single agent had few of the adverse effects of conventional chemotherapy and had anti-tumour activity in cancers in carriers of BRCA1 or 2 mutations [**S2**]. Follow up phase II studies conducted in centres across Europe and the USA provided "positive proof-of-concept" of the tolerability and efficacy of the PARP inhibitor in advanced breast and ovarian cancers in patients carrying mutations of BRCA1 or 2 [**S3**]. The latest report from a phase II clinical trial (BioMarin, compound BMN 673) demonstrated clinical benefit response rates of 82% (23 of 28 ovarian cancer patients) and 67% (12 of 18 breast cancer patients) [**S4**]. Six phase III trials (breast and ovarian cancer) have started or will start before the end of 2013 and regulatory approval of a drug (PARP inhibitor) is anticipated with three years [**S5**].

The research has **expanded the utility of an existing clinical technology,** the BRACAnalysis test that can now be used to identify responders and non-responders to therapy. Previously, BRCA2 status was simply an indicator of disease (breast/ovarian cancer) susceptibility. Now the test can be used to determine which therapy (*i.e.* use of PARP inhibitor or not) could be effective, thus the **effectiveness of a marker of disease has been enhanced.** Nasdaq-listed Myriad Genetics Inc. developed the BRACAnalysis test in 1996 to confirm the presence of BRCA1 and 2 gene mutations that confer risks of up to 87% and 44% for developing breast or ovarian cancer respectively by the age of 70. Myriad Genetics now collaborate with AstraZeneca to stratify patients based on BRACA status on its clinical programme for olaparib development (Phase III

clinical trials) [**S6**]. Myriad Genetics is a leading international diagnostics company with headquarters in Europe and North America.

As a direct result of the Helleday discovery, **industry has invested in research and development** and **new products and services are in production** and **jobs have been created and protected**. The University of Sheffield has benefited financially from the sale of a patent licence to Cambridge-based KuDOS for an initial fee of [text removed for publication] and total payments from the licence are currently at [text removed for publication]. At the time of sale the number of employees at KuDOS was listed as 75. AstraZeneca acquired KuDOS for $210m and the subsidiary now benefits from the pre-clinical and clinical programs of the larger organisation, while AstraZeneca has significantly increased the strength of its DNA-repair product platform. Meanwhile, there are now eight small molecule PARP inhibitors in clinical trials resulting from related drug discovery programs by leading pharmaceutical companies including Rucaparib (Pfizer/Clovis Oncology), Veliparib (Abbott), BMN 673 (BioMarin) and MK4827 (Merck) [**S7**]. All of these research programmes in targeted therapy stem from the initial Helleday discovery; that has also stimulated a whole new area of cancer biology – looking for other targets that exploit synthetic lethality. There has been significant investment in identifying and developing diagnostic tests to identify patients with mutations in DNA-repair genes other than BRCA that may respond to PARP inhibitors. For example, Foundation Medicine specialises in cancer genomics to tailor diagnosis and treatment and is in collaboration with Clovis Oncology [**S8**]. The proof-of-concept demonstration of clinical trials, that breast and ovarian cancers harbouring BRCA mutations respond to PARP inhibitors, has therefore **influenced the practice of how a disease processes could be controlled,** by exploiting synthetic lethality [**S9**].

Highly skilled people have taken up specialised roles in companies and healthcare organisations. Further phase I, II and III trials using PARP inhibitors for the treatment of a wide range of tumours are currently in progress around the world. A simple search of the National Cancer Institute (USA) cancer trials database reveals 92 trials on at least 10 different tumour types recruiting thousands of patients [**S10**]. Included among these trials is the “STOMP” trial (01/2013-01/2015) sponsored by the University of Sheffield and supported by AstraZeneca that tests the use of the PARP inhibitor, olaparib, as a maintenance treatment in Small Cell Lung Cancer.

5. Sources to corroborate the impact

[**S1**] http://www.youtube.com/watch?v=BlOmBa5QG80. The video clip shows and interview with Hope Rugo Clinical Professor, Department of Medicine (Hematology/Oncology); and Director, Breast Oncology Clinical Trials Program, UCSF. It conveys the excitement and enthusiasm that followed the discovery of Helleday and Bryant. The first results from randomized phase II clinical trials with PARP inhibitors on high-risk/late stage breast cancers are summarized following presentation of findings at the 2009 American Society of Clinical Oncology meeting. These PARP inhibitor trials were the first to show a significant survival benefit for cancer patients in a randomized phase II trial of any therapeutic agent and, similarly, the first where a single agent administered via an oral route demonstrated a clinical response.

[**S2**] Fong, P.C.; Boss, D.S.; Yap, T.A.; Tutt, A.; Wu, P.; Mergui-Roelvink, M.; Mortimer, P.; Swaisland, H.; Lau, A.; O'Connor, M.J.; Ashworth, A.; Carmichael, J.; Kaye, S.B.; Schellens, J.H.; de Bono, J.S. (2009). Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. *New England Journal of Medicine*, 361: 123-34. doi: 10.1056/NEJMoa0900212 A clinical phase I trial with oral olaparib is described. Anti-tumour activity was observed only in BRAC1/2 mutation carriers and olaparib has few of the adverse effects of standard chemotherapy.

[**S3**] Tutt, A.; Robson, M.; Garber, J.E.; Domchek, S.M.; Audeh, M.W.; Weitzel, J.N.; Friedlander, M.; Arun, B.; Loman, N.; Schmutzler, R.K.; Wardley, A.; Mitchell, G.; Earl, H.; Wickens, M.; Carmichael, J. (2010) Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof-of-concept trial. *Lancet*, 376: 235-44. doi: 10.1016/S0140-6736(10)60892-6 Results of a phase II trial with oral olaparib and women with BRAC1/2 deficient breast cancers are described and highlight the favourable therapeutic index obtained. An article from the same group follows detailing results of phase II trials with oral olaparib as a monotherapy that demonstrate a clinical response in patients with BRCA1/2 mutated, heavily pre-treated, recurrent, ovarian cancers.

[**S4**] The link http://investors.bmrn.com/releasedetail.cfm?ReleaseID=768635 provides details of the results of phase I and II trials of BMN673. On this page there is also a link to a poster presented at the 2013 American Society of Clinical Oncology Annual Meeting (http://www.bmrn.com/pipeline/clinical-trials/asco.php).

[**S5**] PARP inhibitors bounce back. *Nature reviews drug discovery*/news and analysis: doi: 10.1038/nrd4147

[**S6**] http://investor.myriad.com/releasedetail.cfm?ReleaseID=788489. This link gives details of the collaboration between Myriad Genetics and AstraZeneca to use BRACAnalysis as a companion diagnostic in olaparib phase III clinical trials.

[**S7**] Curtin, N.; Szabo, C. (2013). Therapeutic applications of PARP inhibitors: anticancer therapy and beyond. *Molecular aspects of medicine*. In press. Corrected proof: doi: 10.1016/j.mam.2013.01.006. This review, first published on-line in early 2013, summarises current and potential clinical translation of PARP inhibitors.

[**S8**] http://tinyurl.com/cg3zrqy This link provides details of the collaboration between Foundation Medicine and Clovis Oncology.

[**S9**] http://tinyurl.com/pbrvap3 This link illustrates the magnitude of the step-change in approach to cancer management following the demonstration of PARP-inhibitor induced synthetic lethality in tumours with BRCA1 mutations.

[**S10**] http://clinicaltrials.gov/ct2/results?term=PARP+inhibitor&Search=Search. Clinicaltrials.gov is a service of the US National Institute of Health and lists all public and privately funded clinical trials around the world involving human participants.