Institution: University of Sheffield		
Unit of Assessment: A-05 Biological Sciences		
Title of case study: PARP inhibitors as a therapeutic to treat BRCA-defective cancers		
Period when the underpinning research was undertaken: 2003–2010		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s): Helen Bryant	**Role(s) (e.g. job title):** Lecturer	**Period(s) employed by submitting HEI:** 2003–present
Period when the claimed impact occurred: 2014–2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact (indicative maximum 100 words)

Sheffield research has contributed to the development of a novel tailored therapy for multiple forms of cancer. The selective killing of a tumour using an inhibitor of a DNA repair enzyme (PARP) to induce synthetic lethality was a milestone of personalised cancer therapy. The discovery was patent protected and development rights sold to AstraZeneca. Following a successful clinical trial, the resultant drug was licenced worldwide. Disclosure of the findings stimulated intense investment by Merck and GSK. It has become AstraZeneca's 4th most profitable treatment, generating over £1 billion in sales. Currently four PARP inhibitors are clinically approved for cancers that previously had few treatment options and have increased progression-free survival time for patients in 73 countries.

2. Underpinning research (indicative maximum 500 words)

BRCA2, PARP inhibition and Synthetic Lethality

Cancer remains one of the major challenges in global healthcare. In 2005, Dr Bryant and colleagues discovered that cells that had a loss of function in BRCA2 (a gene associated with a spectrum of cancers) were susceptible to inhibitors of poly(ADP-ribose) polymerase (PARP), leading to cell death [**R1**]. Since both PARP and BRCA are DNA repair enzymes, the team proposed that cancer cells are dependent upon two DNA repair pathways in order to continue to replicate and grow. One pathway requires the PARP enzyme and the second depends upon BRCA2, with the pathways providing redundancy in case one of the pathways fails. By treating BRCA-deficient cells with PARP inhibitors, both pathways are lost and the cancer cell dies, a concept known as synthetic lethality. Using a mouse model, the work in [**R1**] demonstrated this proof of principle. This was the first evidence of synthetic lethality as a therapeutic agent and has led to multiple drugs based around PARP-inhibitors being developed for use in multiple types of cancer.

Mechanistic studies

To underpin the impact of their breakthrough discovery, the Sheffield team performed a series of investigations to understand the mechanism of action of PARP inhibitors.

It was known that BRCA2 is required for the process of homologous recombination (HR). In [**R1**] it was demonstrated that loss of other HR genes also led to synthetic lethality with PARP inhibitors, pointing to a general relationship between PARP and HR. [**R3**] revealed that, in the absence of any exogenous DNA damage, a cell relies on HR to survive when DNA replication forks collapse. This collapse can be caused by disruption of single strand break repair (SSBR) and PARP is required for SSBR, thus providing insight into the potential mechanism of action of PARP inhibitors.

Bryant also demonstrated that PARP is required for stabilising DNA replication forks [**R4**]. Therefore, inhibiting PARP leads to fork instability and a greater requirement for HR, indicating a further mechanism by which PARP inhibitors induce synthetic lethality. The trapping of PARP at replication forks provides an important insight into the mechanism of PARP inhibitors.

In [**R5**] Bryant showed that HR defective cells have hyperactivated PARP, a finding that has led to studies on PARP as a biomarker in cancer treatment. Other synthetic lethal relationships with PARP have also been demonstrated. For example, Ataxia-Telangiectasia Mutated (ATM) was shown to be activated in PARP inhibited cells, with ATM-deficient cells dying upon PARP inhibition **[R6]**. ATM has been linked to T-cell prolymphocytic leukaemia, mantle cell lymphoma, and B-cell chronic lymphocytic leukaemia, suggesting that these might also be suitable targets for PARP inhibitor therapy [**R6**].

Patenting PARP inhibitors

The University of Sheffield filed a patent application in July 2003 for the use of PARP inhibitors as a targeted therapy for tumours occurring in individuals with BRCA2 mutations [**R2**]. The patent has been granted in 32 countries including the UK, US and Japan. Initially licensed to KUDOS therapeutics who developed the PARP inhibitor *Olaparib*, the area was subsequently developed by AstraZeneca after acquiring KUDOS therapeutics in 2006.

3. References to the research (indicative maximum of six references)

University of Sheffield researchers from this unit in bold

R1. **Bryant, H. E.,** Schultz, N., Thomas, H. D., Parker, K. M., Flower, D., Lopez, E., Kyle, S., Meuth, M., Curtin, N. J., & Helleday, T. (2005). Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. *Nature, 434*(7035), 913–917. https://doi.org/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**. Publication date, 10/02/2005.

In order to prevent disclosure of the invention, a large amount of this research was embargoed and publication delayed until after the relevant patent [R2] was finalised.

R3. Saleh-Gohari, N., **Bryant, H. E.**, Schultz, N., Parker, K. M., Cassel, T. N., & Helleday, T. (2005). Spontaneous Homologous Recombination Is Induced by Collapsed Replication Forks That Are Caused by Endogenous DNA Single-Strand Breaks. *Molecular and Cellular Biology, 25*(16), 7158–7169. https://doi.org/10.1128/mcb.25.16.7158-7169.2005

R4. **Bryant, H. E.**, Petermann, E., Schultz, N., Jemth, A.-S., Loseva, O., Issaeva, N., Johansson, F., Fernandez, S., McGlynn, P., & Helleday, T. (2009). PARP is activated at

stalled forks to mediate Mre11-dependent replication restart and recombination. The *EMBO Journal, 28*(17), 2601–2615. https://doi.org/10.1038/emboj.2009.206

R5. Gottipati, P., Vischioni, B., Schultz, N., Solomons, J., **Bryant, H. E.,** Djureinovic, T., Issaeva, N., Sleeth, K., Sharma, R. A., & Helleday, T. (2010). Poly(ADP-Ribose) Polymerase Is Hyperactivated in Homologous Recombination–Defective Cells. *Cancer Research, 70*(13), 5389–5398. https://doi.org/10.1158/0008-5472.can-09-4716

R6. **Bryant, H. E.** & **Helleday, T.** (2006). Inhibition of poly (ADP-ribose) polymerase activates ATM which is required for subsequent homologous recombination repair. *Nucleic Acids Research, 34(*6), 1685–1691. https://doi.org/10.1093/nar/gkl108

4. Details of the impact (indicative maximum 750 words)

Following successful phase II and III clinical trial completion using PARP inhibitor research from Sheffield, AstraZeneca was granted first in class drug status for Olaparib (*Lynparza*®). Since then, the status has been applied to eighteen versions of the PARP inhibitor, four of which are directly attributed to the Sheffield Patent: *Lynparza*®, Niraparib, Rucaparib and Talazaparib [**S1**]. [Text removed for publication].

Building on those initial applications of PARP inhibitors, this work has led to a step-change in the development and accessibility of treatments for cancers with few options. In 2020 Nature Milestones cited R1 as a milestone in cancer research for personalised therapeutics [**S3**].

In 2014, *Lynparza*® became the world's first PARP inhibitor approved for use in America and Europe [**S4**]. This success led to further AstraZeneca investment, launching a collaboration with Merck (MSD UK) to develop treatments for additional cancers with a BRCA mutation. *Lynparza*® has now had positive phase III trial results in four different tumour types: pancreatic and prostate, as well as ovarian and breast [**S5**].

Initially indicated for the treatment of ovarian cancer, the successful trials led to *Lynparza*® expanding to further patient groups in 2017. It is now being prescribed by physicians in 73 countries for the treatment of multiple cancer types. This has increased progression-free survival time for an additional 15,000 patients [**S6**].

Economic impact

Sales of *Lynparza*® in the census period have continued to increase each year and have exceeded $1.2 billion in 2020 [**S6**]. AstraZeneca developed a strategic oncology collaboration with MSD UK to expand the uses of *Lynparza*® to other forms of cancer [**S7**]. This collaboration, which involved MSD UK buying 50% of *Lynparza*® for $8.5 billion, has achieved phase III clinical trial success in BRCA-mutated pancreatic cancer, which has the worst survival rate of all common cancers [**S5**]. The collaboration went on to work with Myriad Genetics Inc on their BRACAnalysis CDx test to identify BRCA mutations in patients. This test is now used in the USA and Japan to better target PARP inhibitor treatment [**S7**].

The sublicensed patent enabled other companies to produce PARP inhibitors for additional cancer types. Tesaro's agreement with AstraZeneca contributed to the development of Niraparib launched in 2016 for the treatment of ovarian, fallopian tube and primary peritoneal cancers **[S9]**. In January 2019, GSK bought Tesaro, for $5.1 billion, to strengthen their commercial oncology capability [**S8**].

Increased survival of cancer patients worldwide

Germline BRCA1 and BRCA2 mutations account for 72% and 69% breast cancers in women by the age of 80. The BRCA1 mutation increases the risk of ovarian cancer from 1.3% to 44%, and for BRCA2 mutations the risk increases to 17%. BRCA mutations also increase the risk of breast cancer in men as well as increasing the risk of prostate and pancreatic cancer. Clinical trials with PARP inhibitors have been shown to delay progression by an average of 3 months compared to chemotherapy [**S5**].

Olaparib (*Lynparza*®) was approved for use in Europe (EMA) and the USA (FDA) in December 2014 and Japan in July 2018. In 2015, NICE approved the use of Olaparib and Niraparib for NHS ovarian cancer patients, who had had three or more courses of chemotherapy, through the National Cancer Drug Fund [**S4**].

In 2018, Olaparib became available through NHS prescription as a first-line maintenance therapy in BRCA-mutated, advanced ovarian, fallopian tube and peritoneal cancer. Olaparib also became the first FDA-approved treatment for patients with gBRCAm HER2-negative metastatic breast cancer [**S4**].

The phase III POLO trial explored the efficacy of *Lynparza*® as 1st-line maintenance monotherapy in patients with gBRCAm metastatic pancreatic cancer whose disease has not progressed on platinum-based chemotherapy. The trial determined that the median progression-free survival was significantly longer in the treatment group. POLO is the first positive phase III trial of any PARP inhibitor in a disease where there is a critical unmet medical need **[S5]** and has resulted in FDA approval for *Lynparza*® in the US for the maintenance treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated pancreatic cancer [**S4**].

The AstraZeneca sublicensing of the Sheffield patent has led to the development of PARP inhibitors from other pharmaceutical companies for use as treatment of BRCA-mutated ovarian, fallopian tube, primary peritoneal and BRCA mutated breast cancers. Niraparib (GSK) and Talazoparib (Pfizer) have been approved for use in America since 2018 and Rucaparib (Clovis Oncology) was approved for use in America and Europe in 2019 **[S1].**

In Europe, the use of PARP inhibitors has been extended to ovarian, fallopian tube or peritoneal cancers to delay the next cycle of platinum chemotherapy, as well as to increase survival **[S4].**

5. Sources to corroborate the impact (indicative maximum of 10 references)

S1. Drug approvals report 2014-2020.

S2. [Text removed for publication].

S3. Nature Milestones 2005 cited R1 as a milestone in cancer research for personalised therapeutics (https://www.nature.com/immersive/d42859-020-00083-8/index.html).

S4. Regulatory approvals: UK NICE Guidance (TA598), Aug 2019 (https://www.nice.org.uk/guidance/ta598); USA FDA approvals for *Lynparza*® from Dec 2014 to May 2020 (https://bit.ly/38yxkIu) and Europe EMA list of approval from Dec 2014 to May 2020 (http://bit.ly/30EoVPp).

S5. List of *Lynparza*® trials and results showing increased progressions free survival (http://bit.ly/38AYhLl); SOLO Trial Results (Moore, K., et. al. (2018). Maintenance Olaparib

in Patients with Newly Diagnosed Advanced Ovarian Cancer. *New England Journal of Medicine, 379*(26), 2495–2505. https://doi.org/10.1056/nejmoa1810858) and POLO Trial Results (Golan, T. et. al. (2019). Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer. *New England Journal of Medicine, 381*(4), 317–327. https://doi.org/10.1056/nejmoa1903387).

S6. Annual report of sales for AstraZeneca which contains *Lynparza*® sales to Q3 2020 (https://www.astrazeneca.com/content/dam/az/PDF/2020/q3/Year-to-date_and_Q3_2020_results_announcement.pdf).

S7. AstraZeneca and Merch (MSD UK) with Myiad sponsored the POLO trial and BRACAnalysis CDx testing to be used in selecting patients for treatment (http://bit.ly/30EpwAD and http://bit.ly/2OsjwIL).

S8. GSK Press release about buying Tesaro (http://bit.ly/3rWd8rX).

S9. Statement on the licensing agreement and payment conditions with AstraZeneca, page 87 under technology licenses (http://ir.tesarobio.com/node/10061/html).