Institution: Newcastle University

Unit of Assessment: 8

Title of case study: Discovery of PARP inhibitors for cancer treatment – Rucaparib

Period when the underpinning research was undertaken: 2000-2004

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Bernard Golding	Professor of Organic Chemistry	1983-present

Period when the claimed impact occurred: 2014-2020

Is this case study continued from a case study submitted in 2014? Y

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

Rucaparib (Rubraca™) is a poly (ADP-ribose) polymerase 1 (PARP1) inhibitor used worldwide to treat advanced ovarian cancer, a previously untreatable disease. The drug was discovered by Newcastle medicinal chemists with Agouron pharmaceuticals and approved for use in the USA (2016) and Europe (2018). Rubraca has treated >9,000 patients and has generated worldwide sales of >$375M to date. It is distributed free of charge under the Rubraca Patient Assistance Program (USA), and is available through the Cancer Drugs Fund (UK). Rubraca has given significant economic benefit to Clovis Oncology including the employment of ~400 people. Two other licenced PARP drugs – niraparib and veliparib with $400M sales – have structures based on Newcastle chemistry.

2. Underpinning research (indicative maximum 500 words)

Discovery of rucaparib
Newcastle research in collaboration with Cancer Research UK and Agouron Pharmaceuticals led to the development of rucaparib: the first-in-class PARP inhibitor (PARPi) [P1-4]. The principal contributions from chemistry research since 2000 were the optimisation of the physicochemical properties of the benzimidazole carboxamides to make them suitable for clinical use, directed by the Newcastle chemistry team (Griffin and Golding 2000-2004). The chemistry team used a structure-directed drug design strategy using crystal structures of the inhibitors bound to the PARP1 protein that resulted in the identification of key compounds, e.g. NU1085, with *in vivo* potency [P1]. A collaboration between Agouron and Newcastle chemists extended this work through the design and synthesis of tricyclic PARP inhibitors [P2-4]. Extensive synthetic medicinal chemistry efforts by Agouron and Newcastle scientists produced libraries of inhibitors based on a number of rationally designed tricyclic scaffolds. Detailed evaluation of the *in vitro* and *in vivo* properties of these libraries allowed the selection of rucaparib as the ideal compound for first-in-class clinical trials.
Rucaparib was the first PARPi to enter clinical trials, with the first dose being given in Newcastle.

Homologous repair, PARP1 inhibition and rucaparib
BRCA genes encode tumour suppressor proteins which repair DNA double strand breaks. Mutations in *BRCA* genes lead to errors in DNA repair and the cells becoming homologous repair deficient (HRD) enabling tumour development. Although HRD tumours lack DNA repair via homologous recombination they retain the PARP1 (poly ADP ribose polymerase) enzyme which repairs single strand breaks, supporting tumour maintenance. Thus, PARP1 inhibition leaves HRD-deficient cells without a functioning DNA-repair mechanism, and so results in highly specific cytotoxicity. This process is termed synthetic lethality. BRCA1 and BRCA2 mutations are known to increase the risk of breast and ovarian cancer in women and have also been observed to increase the risk of other cancers including fallopian tube and peritoneal cancer in

women and prostate cancer in men. Prostate cancer in particular is the most common cause of cancer death in UK men. The presence of *BRCA* mutations increases the risk of prostate cancer by 1.82 (BRCA1) and 4.65 (BRCA2) especially in patients below 65 years old.
Research suggested that acquired somatic BRCA mutations and other homologous recombination repair (HRR) pathway defects result in homologous repair deficient tumours (HRD) in >50% of ovarian cancers. Newcastle tested the sensitivity of HRD primary ovarian cancer cultures to rucaparib showing that 92.8% of HRD cultures were sensitive to rucaparib and had a 2-fold reduction in cell survival. HRR-competent cultures showed 0% response to rucaparib and remained viable {2010*Clin.CancerRes.*2344}. Additionally, HRR status correlated with survival clinically in platinum treated patients with either ovarian or non-ovarian cancer. This suggested a potentially wider application of PARPi in other cancer types {2012*CancerRes.*5675}. Subsequent success in ovarian cancer clinical trials (involving Newcastle and detailed in section 4) led Clovis Oncology, the worldwide licence holders of rucaparib (marketed as Rubraca™), to expand the scope of rucaparib to other cancers suggested to be caused by *BRCA* mutations.

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

All research peer reviewed; citations as per Web of Science 12/3/21

[**P1**] A W White, R Almassy, A H Calvert, N J Curtin, R J Griffin, Z Hostomsky, K Maegley, D R Newell, S Srinivasan, and **B T Golding**, Resistance-modifying agents. 9. Synthesis and biological properties of benzimidazole inhibitors of the DNA repair enzyme poly(ADP-ribose)polymerase (PARP), *J Med Chem*, 2000, 43, 4084-4097 (DOI: 10.1021/jm000950v). Citations: 247.

[**P2**] S S Canan Koch, L H Thoresen, J G Tikhe, K A Maegley, J Li, X.-H Yu, S E Zook, R A Kumpf, C Zhang, R N Mansour, K E Zhang, A Ekker, C R Calabrese, N J Curtin, H D Thomas, L-Z Wang, A H Calvert, **B T Golding**, R J Griffin, S E Webber, and Z Hostomsky, Novel tricyclic poly(ADP-ribose) polymerase-1 inhibitors with potent anticancer chemopotentiating activity: design, synthesis, and X-ray cocrystal structure, *J Med Chem*, 2002, 45, 4961-4974 (DOI: 10.1021/jm02059n). Citations: 114

[**P3**] D J Skalitzky, J T Marakovits, K A Maegley, A Ekker, X H Yu, Z Hostomsky, S E Webber, B W Eastman, R Almassy, J K Li, N J Curtin, D R Newell, A H Calvert, R J Griffin, and **B T Golding**, Tricyclic benzimidazoles as potent poly(ADP-ribose) polymerase-1 inhibitors, *J Med Chem*, 2003, 46, 210-213 (DOI: 10.1021/jm0255769). Citations: 139

[**P4**] Tikhe JG, Webber SE, Hostomsky Z, Maegley KA, Ekkers A, Li JK, Yu XH, Almassy RJ, Kumpf RA, Boritzki TJ, Zhang C, Calabrese CR, Curtin NJ, Kyle S, Thomas HD, Weng LZ, Calvert AH, **Golding BT**, Griffin RJ, Newell DR. Design, synthesis, and evaluation of 3,4-dihydro-2H-[1,4]diazepino[6,7,1-hi]indol-1-ones as inhibitors of poly(ADP-ribose) polymerase, *J Med Chem*, 2004, 47, 5467-5481 (DOI: 10.1021/jm030513r). Citations: 43

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

The impact generated by this first-in-class PARP inhibitor (Rubraca™; rucaparib), a product of Newcastle Chemistry research, can be summarised as: **healthcare** impact resulting from successful Phase II/III trials and licensing of the drug producing improved clinical practice and patient benefits, including approval in other cancers (e.g. prostate cancer); **economic** impact from sales of the drug; and **technological** impact from the discovery of a new class of cancer drugs. It is a continuation of the REF2014 case study "Development of the first-in-class poly(ADP-ribose) polymerase-1 (PARP-1) inhibitor rucaparib for the treatment of cancer" that described the impact up to Phase II clinical trials.

Healthcare Impact – Changes to Clinical Practice
Since 2014, rucaparib has secured multiple regulatory approvals for ovarian, fallopian tube, peritoneal and prostate cancer from the US Food and Drug Administration (FDA), European

Medicines Agency (EMA) and the UK National Institute for Health and Care Excellence (NICE) through the Cancer Drug Fund (Figure 1) [E1]. Rucaparib is also the only PARPi drug to receive regulatory approval for the treatment of cancers caused by both germline and somatic mutations thus expanding its clinical use. This accelerated regulatory progress demonstrates the lack of other effective treatments for these cancers.

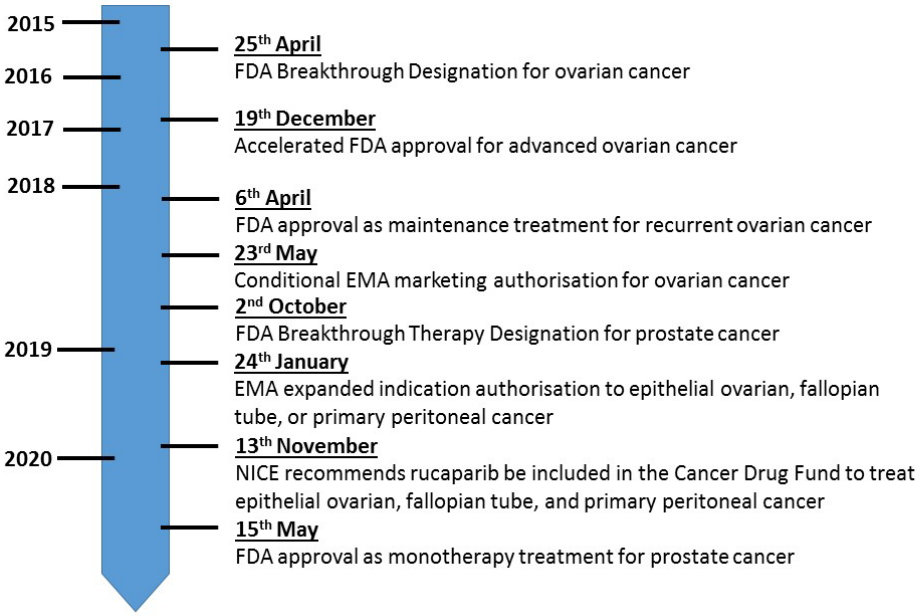

Figure 1: Timeline of approval of rucaparib by international organisations in the REF period

Healthcare Impact – Patient benefit

BRCA1 and BRCA2 mutations are known to increase the risk of breast and ovarian cancer in women and have also been observed to increase the risk of other cancers including fallopian tube and peritoneal cancer in women {2003*JClinOncol*4222} and prostate cancer in men {2007*BrJCancer*11, 2015*HeredCancerClinPract*16} (Table 1). Ovarian cancer is the eighth most common cancer among women with ~295,000 new cases in 2018 {2020*The Oncologist*109}. Prostate cancer is the most common cause of cancer death in UK men. The breadth of cancers caused by *BRCA* mutations significantly increases the population of cancer patients who are potential candidates for treatment with rucaparib.

Table 1: UK statistics for ovarian and prostate cancer (source Cancer Research UK)

Cancer	Total annual UK incidence in 2017 (rate per 100,000)	Risk of cancer based on BRCA mutations	
		BRCA1	BRCA2
Ovarian	11.7	47-63%	27%
Prostate	79.1	1.82%	2.5-4.65%

Rucaparib, the first in class PARP1 inhibitor, pioneered the novel concept of targeting DNA-repair to induce synthetic lethality in tumour cells that have defective DNA-repair pathways [E2,3]. The ability to specifically target BRCA deficient cancers with this approach has led to significant patient benefit. Thus, it has led to a whole new area of cancer chemotherapy targeting DNA-repair and the DNA damage response.

Approximately 9,000 patients have received rucaparib in clinical trials to date: ~2,800 between the Study 10 (N=136), ARIELs 2, 3 and 4 (N=493, 564 and 345 respectively), ATHENA (N=1000) and TRITON2 (N=360) trials and a further 6,380 on other international trials [E4; E5; E6]. The ARIEL3 trial in ovarian cancer showed rucaparib increased progression free survival by between 5.4 and 11.2 months (Table 2){2017*Lancet*1949}.

Table 2: Results from the ARIEL3 trial.

Ovarian Patients	Progression free survival (median in months)	
	Placebo	Rucaparib
All	5.4	10.8
BRCA mutant		13.6
HRD deficient		16.6

The TRITON2 trial in prostate cancer showed rucaparib produced responses in 44% of patients with a duration of response ranging from 1.7-24+ months (>50% responded for >6 months) [E7]. This data informed the FDA approval of rucaparib for castration resistant prostate cancer [E8]. The synthetic lethality approach results in highly targeted tumour toxicity, leaving normal tissues unaffected. As a result, the side-effect profile of rucaparib is relatively mild compared to conventional chemotherapy and patients treated with rucaprib have a good quality of life.

Economic impact from sales of rucaparib

In 2011, the worldwide rights of Rucaparib were sublicensed to Clovis Oncology by Pfizer. Following approval in the USA (2015), the EU (2018) and the UK (2019), sales of Rucaparib have grown year on year (Figure 2); since 2016 sales of Rucaparib have resulted in a net product revenue of >$375M for Clovis Oncology [E9]. This equates to over 43,000 units of Rucaparib sold. Additionally, Clovis provides ~20% of the US commercial supply of rucaparib free of charge to eligible patients in the US under its Patient Assistance Programme - the equivalent of a further $82.3M or ~9400 units [E6].

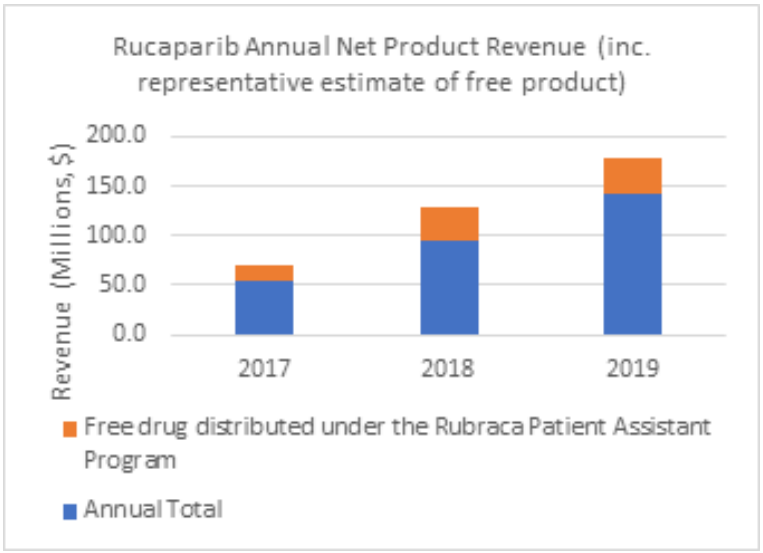

Figure 2: Rucaparib sales 2017-2019

Technological Impact

The discovery of rucaparib, pioneered by Newcastle, has stimulated PARP research worldwide leading to other potent inhibitors based on the same benzimidazole carboxamide pharmacophore. Notably niraparib (Tesaro) {2015JMC3302} which received FDA approval in 2017, and veliparib (Abbott) {2007ClinCanRes2728}. Both drugs have core structures that display the same PARP inhibitory pharmacophore as seen in the original Newcastle benzimidazole carboxamides, described in the 2000 paper [P1] and preceding patents. There are currently an additional 4 PARP inhibitors currently in clinical trials (e.g. NCT01472783, NCT01286987, NCT01945775, and NCT03863860).

The impact of this work to medicinal chemistry and drug design has been recognized by the awards given to the researchers involved. In 2010, the PARP research team, including Griffin and Golding won the Cancer Research UK's Translational Cancer Research Prize for the discovery of rucaparib. In 2014, Griffin was awarded the RSC George and Christine Sosnovsky Award in Cancer Therapy and, in 2019, Golding won the RSC Robert Robinson Award for broad and substantial contributions to synthetic and mechanistic organic chemistry directed to

biochemistry, microbiology and medicine including understanding how DNA repair led to the anticancer drug rucaparib.

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

E1. Details of regulatory approvals granted since 2014 by: US Food and Drug Administration (available: https://www.fda.gov/drugs/resources-information-approved-drugs/rucaparib), European Medicines Agency (available: https://www.ema.europa.eu/en/medicines/human/EPAR/rubraca), and the UK National Institute for Health and Care Excellence (available: https://www.nice.org.uk/guidance/ta611)

E2. Paper detailing in vitro and in vivo activity of rucaparib in tumours with BRCA mutation: Drew Y, Mulligan EA, Vong WT, Thomas HD, Kahn S, Kyle S, Mukhopadhyay A, Los G, Hostomsky Z, Plummer ER, Edmondson RJ, Curtin NJ. (2011) Therapeutic potential of poly(ADP-ribose) polymerase inhibitor AG014699 in human cancers with mutated or methylated BRCA1 or BRCA2. J Natl Cancer Inst. 103(4):334-46. doi: 10.1093/jnci/djq509 Citations: 175.

E3. Paper detailing first clinical trial with rucaparib in tumours carrying a BRCA mutation: Drew Y, Ledermann J, Hall G, Rea D, Glasspool R, Highley M, Jayson G, Sludden J, Murray J, Jamieson D, Halford S, Acton G, Backholer Z, Mangano R, Boddy A, Curtin N, Plummer R. (2016) Phase 2 multicentre trial investigating intermittent and continuous dosing schedules of the poly(ADP-ribose) polymerase inhibitor rucaparib in germline BRCA mutation carriers with advanced ovarian and breast cancer. British Journal of Cancer, 114(7):723-30. doi: 10.1038/bjc.2016.41. Citations: 19

E4. Details of the completion of the enrollment of the ATHENA clinical trial, identifying 1000 patients as having been enrolled, available from: https://ir.clovisoncology.com/investors-and-news/news-releases/press-release-details/2020/Clovis-Oncology-Announces-Completion-of-Target-Enrollment-in-the-ATHENA-Trial-a-Phase-3-Maintenance-Treatment-Study-in-Front-line-Newly-Diagnosed-Advanced-Ovarian-Cancer/default.aspx

E5. PDF detailing a search of clinicaltrials.org, a database of all clinical trials worldwide, detailing all patients enrolled on trials and being treated with rucaparib.

E6. Testimonial Letter from Clovis Oncology, confirming the importance of the Newcastle research to the development of Rucaparib, key dates in the REF period, and impact on the company, including sales of Rucaparib and patients treated in trials to date.

E7. Paper detailing preliminary results of the TRITON2 clinical trial, showing the positive effects on patients: Abida et al, 846PD - Preliminary results from the TRITON2 study of rucaparib in patients (pts) with DNA damage repair (DDR)-deficient metastatic castration-resistant prostate cancer (mCRPC): Updated analyses, 2019, Annals of Oncology, (30), Pages v327-v328, doi:10.1093/annonc/mdz248

E8. Clovis Press Release detailing FDA breakthrough designation of Rucaparib for castration resistant prostate cancer, available from: https://s22.q4cdn.com/778348918/files/doc_news/Clovis-Oncology-Receives-Breakthrough-Therapy-Designation-for-Rubraca-rucaparib-for-Treatment-of-BRCA12-Mutated-Metastatic-Castration-Resistant-Prostate-Cancer-mCRPC.pdf

E9. Net product revenue of Rucaparib sales, calculated from combined Clovis Oncology operating reports (annual reports for 2016, 2017, 2018, 2019 and 2020 2nd Quarter operating results), available on request.