Institution: Newcastle University

Unit of Assessment: UoA1

Title of case study: The development of a novel class of anticancer drugs, PARP inhibitors, has attracted multi-million dollar investments in clinical trials by nine pharmaceutical companies

1. Summary of the impact

Newcastle research selected the DNA repair enzyme poly(ADP-ribose) polymerase (PARP) as a promising target for cancer therapy. The first-in-class PARP inhibitor, rucaparib, was developed at Newcastle, in collaboration with Cancer Research UK and Agouron Pharmaceuticals, and subsequently became the first PARP inhibitor to be used to treat a cancer patient in a clinical trial. Currently, at least 8 PARP inhibitors are being developed and major pharmaceutical companies have to date invested around $385 million in clinical trials, and over 7,000 patients worldwide have been treated with PARP inhibitors in trials since 2008, demonstrating the importance of basic and translational research in universities to drug discovery by pharmaceutical companies.

2. Underpinning research

Key Newcastle researchers and their roles at the time of the research
(Where people left/joined the university in the period 1993-2013, years are given in brackets)

AH Calvert (1990-2009), professor of medical oncology; NJ Curtin, lecturer/senior lecturer 1998-2006, then professor of experimental cancer therapeutics; BW Durkacz (1982-2010) was the project originator; she was a reader 1984-2008, then professor of experimental cancer therapeutics; BT Golding, professor of organic chemistry 1983-2006, then senior research investigator; RJ Griffin, reader in cancer therapy 1991-2001, then professor of medicinal chemistry; DR Newell, professor of cancer therapeutics; R Plummer (2001 onwards), clinical lecturer 2001-2004, clinical senior lecturer of oncology 2004-2008, then clinical professor of experimental cancer medicine.

Background
DNA repair pathways can enable cancerous cells to survive the DNA damage induced by radiation therapy and chemotherapy. Thus, inhibitors of these pathways could enhance the effect of these treatments. Basic research at Newcastle instigated by Prof Barbara Durkacz selected the DNA repair enzyme poly(ADP-ribose) polymerase (PARP) as a promising target for cancer therapy. Multiple pathways contribute to the repair of DNA and PARP is a key enzyme in the repair pathway. Early PARP inhibitors, the benzamides, were developed in the 1980s, but lacked the potency and specificity required for pre-clinical evaluation.

Research
Since 1995, the work of a multidisciplinary team at Newcastle has resulted in the development of novel and potent PARP inhibitors (1000 times more potent than benzamides) that selectively inhibit the enzyme [R1, R2, R3]. These were developed using structure-based drug design, in collaboration with Agouron Pharmaceuticals and Cancer Research UK. The chemo- and radio-potentiating abilities of these inhibitors were evaluated in animal models and cell cultures and they were demonstrated to have a cellular activity that increases the DNA damage induced by cytotoxic anticancer drugs and ionising radiation [e.g. R2].

Cancer Research UK selected the potent PARP inhibitor *rucaparib* (AG014699, CO-338) for clinical trials, and the first cancer patients in the world to receive a PARP inhibitor were treated at Newcastle in 2003 as part of a Phase I study [R4]. With 33 patients, the study demonstrated that rucaparib in combination with the chemotherapeutic drug temozolomide, was well tolerated by patients, and confirmed PARP inhibition in all patients [R4]. Subsequently a Phase II study with 40 patients demonstrated that temozolomide efficacy was increased when used in combination with rucaparib [R5].

In parallel, the research undertaken at Newcastle stimulated widespread interest, both in industry and academia, in PARP as a target in cancer therapies, with more than 10 compounds

subsequently selected for development. In collaboration with Sheffield (Prof Thomas Helleday), the Newcastle group also demonstrated the synthetic lethality of PARP inhibitors towards cells with mutations in the BRCA genes, the underlying cause of many inherited breast and ovarian cancers [R3, R6]. Synthetic lethality is defined as the lethal effect of inactivating two enzymes or pathways when inactivation of either alone is tolerated [6].

3. References to the research

(Newcastle researchers in bold. Citation count from Scopus, July 2013)

R1. **Griffin RJ**, **Srinivasan S**, **Bowman K**, **Calvert AH**, **Curtin NJ**, **Newell DR**, **Pemberton LC**, **Golding BT**. Resistance-modifying agents. 5. Synthesis and biological properties of quinazolinone inhibitors of the DNA repair enzyme poly(ADP-ribose) polymerase (PARP). (1998) Journal of Medicinal Chemistry, 41(26):5247-56. DOI: 10.1021/jm980273t. **Cited by 79**

R2. **Calabrese CR**, Almassy R, **Barton S**, **Batey MA**, **Calvert AH**, Canan-Koch S, **Durkacz BW**, Hostomsky Z, Kumpf RA, **Kyle S**, Li J, Maegley K, **Newell DR**, **Notarianni E**, Stratford IJ, Skalitzky D, **Thomas HD**, **Wang LZ**, Webber SE, Williams KJ, **Curtin NJ**. Anticancer chemosensitization and radiosensitization by the novel poly(ADP-ribose) polymerase-1 inhibitor AG14361. (2004) Journal of the National Cancer Institute, 96:56-67. DOI: 10.1093/jnci/djh005. **Cited by 216**

R3. Bryant HE, Schultz N, **Thomas HD**, Parker KM, Flower D, Lopez E, **Kyle S**, Meuth M, **Curtin NJ**, Helleday T. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. (2005) Nature, 434:913-917. DOI:10.1038/nature03443. **Cited by 982**

R4. **Plummer R**, **Jones C**, Middleton M, Wilson R, Evans J, Olsen A, **Curtin N**, **Boddy A**, McHugh P, **Newell D**, Harris A, Johnson P, Steinfeldt H, Dewji R, Wang D, Robson L, **Calvert H**. Phase I study of the poly(ADP-ribose) polymerase inhibitor, AG014699, in combination with temozolomide in patients with advanced solid tumors. (2008) Clinical Cancer Research, 14:7917-7923. DOI: 10.1158/1078-0432.CCR-08-1223. **Cited by 128**

R5. **Plummer R**, Lorigan P, Steven N, Scott L, Middleton MR, Wilson RH, **Mulligan E**, **Curtin N**, Wang D, Dewji R, Abbattisya A, Gallo J, **Calvert H**. A phase II study of the potent PARP inhibitor, Rucaparib (PF-01367338, AG014699), with temozolomide in patients with metastatic melanoma demonstrating evidence of chemopotentiation (2013) Cancer Chemotherapy Pharmacology, 71:1191–1199. DOI: 10.1007/s00280-013-2113-1. **(Published in May 2013; not yet cited)**

R6. **Drew Y**, **Mulligan EA**, **Vong WT**, **Thomas HD**, **Kahn S**, **Kyle S**, **Mukhopadhyay A**, Los G, Hostomsky Z, **Plummer ER**, **Edmondson RJ**, **Curtin NJ**. Therapeutic potential of poly(ADP-ribose) polymerase inhibitor AG014699 in human cancers with mutated or methylated BRCA1 or BRCA2. (2011) Journal of the National Cancer Institute, 103:334-346. DOI: 10.1093/jnci/djq509. **Cited by 47**

Selected funding awards

- 1993-1996 *The synthesis and evaluation of inhibitors of poly-ADP ribose polymerase and nucleoside transport to potentiate the activity of cytotoxic drugs*. The North of England Cancer Research Campaign - £72,000.
- 1998-2002 *An investigation into the interactive effects of poly (ADP-ribose) polymerase and DNA-dependent protein kinase*. CRUK - £70,016
- 1998-1999 *Poly (ADP) Ribose Polymerase Inhibitors*. Agouron Pharmaceuticals - £531,956.
- 2001-2002 *Development of pharmacodynamic assays for the clinical evaluation of novel PARP inhibitors, and pre-clinical investigations of backup compounds.* Agouron Pfizer GRD - £220,000
- 2002-2003 *NECRC Cancer Research Unit Core Grant*. Cancer Research UK - £504,404
- 2002-2005 *Phase 1 Trial of the Novel PARP Inhibitor, AG14699, in Combination with Temozolomide*. CRUK - £178,595
- 2007-2010 *Therapeutic potential of PARP inhibitors in cancers defective in BRCA1, BRCA2 or other defects contributing to a BRCAness phenotype*. Pfizer Inc. USA - £104,940.61

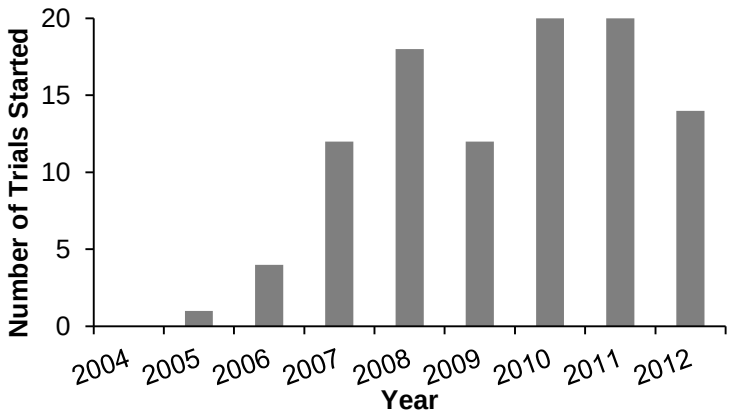
4. Details of the impact

The research initiated at Newcastle in the 1990s not only led to the first in class trial of a PARP inhibitor but also played a key role in establishing the translational research routes of development of this class of agents. When the project was first established, PARP was not considered a viable target, particularly by the pharmaceutical industry, but the Newcastle team championed it and drove the project to clinical proof-of-principle. PARP has now been adopted as a key cancer drug target by the global pharmaceutical industry, and has reached cancer patients across Europe, the Americas, Australasia and Asia, with eight PARP inhibitors currently in clinical trial development worldwide and at least eight cancer types being treated through clinical trials [EV a].

In 2010, Cancer Research UK formally recognised the research underpinning the discovery and development of PARP inhibitors, awarding their inaugural Translational Cancer Research Prize to the Newcastle PARP team. This prize was awarded '…*in recognition of the discovery and development of novel PARP inhibitors, specifically the achievement of the team in driving an initial scientific concept through medicinal chemistry and preclinical work, to first-in-man clinical studies*.' [EV b]. The successful exploitation of PARP as a drug target builds on many decades of basic research on DNA damage and repair by many scientists and clinicians. In so doing, it demonstrates the importance of academia as a resource for new targets in drug discovery. Notably, numerous other DNA damage and repair targets are now being evaluated; based largely on the PARP inhibitor paradigm.

Commercial Impact

The research has had a significant impact on the UK and global pharmaceutical industry, with the following companies investing heavily in clinical trials and clinical PARP inhibitor programmes: AstraZeneca, Clovis, SanofiAventis, Abbott, Merck, Biomarin, Eisai, Cephalon and Genentech [EV a]. It is clear that since the initial Newcastle trial (2003-2005), in which patients were treated with a PARP inhibitor for the first time, and the demonstration of synthetic lethality in BRCA-deficient cancers, there has been a marked increase in the commencement of trials testing PARP inhibitors [data extracted from EV a]:



In the period May 2008- May 2013, 33 cancer trials involving PARP inhibitors were completed and an additional 52 trials are currently open, totalling 50 Phase I, 33 Phase II and 2 Phase III trials in this period [EV a]. In 2011 the average per patient cost associated with a Phase I, II and III trial in Oncology were reported to be $21,883, $73,303 and $65,900 respectively [EV c]. An estimate of the investment by companies into PARP inhibitor trials is summarised in the following table:

Phase	No. of Trials	No. of patients	Average Total cost
I	50	3,173	$69.4 million
II	33	3,160	$231.6 million
III	2	1,299	$85.6 million

Impact on Patients

Since the initial Phase I trial (2003), clinical trials involving PARP inhibitors have enrolled around 7,000 patients (approx. 750 of which were recruited to more than one trial phase), with around 5,600 patients having enrolled in trials opening January 2008 onwards [EV a, d]. From the outset, the potential of PARP inhibitors was clear and two out of the 33 patients treated for malignant melanoma in the Phase I trial and five out of the 40 patients treated in the Phase II trial (2005) (both outlined in Section 2) are today (October 2013) alive and in remission [EV e]. When recruited into the trials, all of these patients were diagnosed with incurable disease with a life expectancy of just a few months.

A recent Phase II trial of the PARP inhibitor *olaparib* in *BRCA*-deficient advanced breast cancer has shown not only that this drug is well tolerated, but also a significant reduction in tumour size in 38% of patients (9 of 24 patients) [EV f]. Similarly, a Phase II trial showed that this drug was well tolerated in *BRCA*-deficient ovarian cancer patients, with 33% (11 of 33 patients) showing reduced tumour size [EV g]. *BRCA* proteins play a major role in the response to and repair of DNA double strand breaks through the *homologous recombination repair* pathway, while PARP inhibitors play a crucial role in DNA single-strand break repair. Harmful mutations in BRCA genes produce a hereditary breast-ovarian cancer syndrome in affected families. According to the National Cancer Institute between 1 in 400 and 1 in 800 women will have a *BRCA* mutation, which equates to a conservative estimate of around 40,000 women (1 in 800) in the UK; of these approx. 60% (24,000 women) will develop breast cancer, and 15-40% (6,000-16,000 women) will develop ovarian cancer. The PARP inhibitor olaparib could therefore have a significant impact on the lives of women diagnosed with breast- or ovarian cancer. Furthermore, PARP inhibitors offer the potential for chemo-prevention, thereby allowing breast cancer patients to avoid disfiguring surgery such as bilateral mastectomy and oophorectomy [EV d]. In addition, a recent small study demonstrated promising results in patients with BRCA mutations after treatment with a new PARP inhibitor, BMN 673; 18 out of 42 (42%) patients with ovarian or breast cancer showed signs of tumour shrinkage after treatment [EV f].

5. Sources to corroborate the impact

EV a. www.clinicaltrials.gov (Search term '*PARP inhibitor*', excluding *withdrawn* and *terminated* trials. For patient numbers, trials *not yet recruiting* were also excluded.)

EV b. Inaugural Cancer Research UK Translational Research Team Prize in 2010 http://www.cancerresearchuk.org/science/funding/find-grant/all-funding-schemes/translational-cancer-research-prize/past-winners/

EV c. http://www.pharmalive.com/clinical-trial-costs-are-rising-rapidly

EV d. Plummer R. Perspective on the pipeline of drugs being developed with DNA damage as a target. Clinical Cancer Research (2010) 16, 4527-4531. DOI: 10.1158/1078-0432.CCR-10-0984

EV e. Patient survival data; corroborating e-mail.

EV f. Tutt, A et al. Phase II trial of the oral PARP inhibitor olaparib in BRCA-deficient advanced breast cancer. Journal of Clinical Oncology, 2009 ASCO Annual Meeting Proceedings (Post-Meeting Edition). Vol 27, No 18S (June 20 Supplement). http://meeting.ascopubs.org/cgi/content/abstract/27/18S/CRA501

EV g. Audeh, MW et al. Phase II trial of the oral PARP inhibitor olaparib (AZD2281) in BRCA-deficient advanced ovarian cancer. Journal of Clinical Oncology, 2009 ASCO Annual Meeting Proceedings (Post-Meeting Edition). Vol 27, No 15S (May 20 Supplement). http://meeting.ascopubs.org/cgi/content/abstract/27/15S/5500