Institution: Newcastle University

Unit of Assessment: UoA 8 Chemistry

Title of case study: Development of the first-in-class poly(ADP-ribose) polymerase-1 (PARP-1) inhibitor Rucaparib for the treatment of cancer

1. Summary of the impact

Newcastle University research discovered the first potent inhibitors of the DNA repair enzyme poly (ADP-ribose) polymerase 1 (PARP-1) through medicinal chemistry and preclinical work leading to first-in-man clinical studies. This research led to the development of Rucaparib, an agent that inhibits the ability of cancer cells to survive drug treatments or radiotherapy. As a result of Newcastle's research a further 8 PARP inhibitors are in development. Major pharmaceutical companies have invested an estimated $385 million in clinical trials, with at least 7000 patients enrolled in PARP inhibitor trials since 2008. Cancer patients worldwide have already been successfully treated with these new anti-cancer drugs.

2. Underpinning research

Although many cancer patients are successfully treated with drugs there is an urgent need for better drugs for some of the most prevalent cancers including breast, ovarian and prostate. Prior to 1993, inhibitors of PARP-1 were studied by *Professor B Durkacz* (*1982-2009 – Professor of Experimental Cancer Therapeutics*; *Northern Institute of Cancer Research (NICR), Newcastle University*), but were of insufficient potency for clinical use. Following these initial observations, a translational research effort was instituted between the NICR and *Golding* (*1983 to date – Professor of Organic Chemistry*) and *Griffin* (*1990 to date – Professor of Medicinal Chemistry*) in the School of Chemistry. After considering the mode of action of PARP-1, we conceived benzimidazole and quinazolinone derivatives as possible effective inhibitors [**P1**, **P2**] A synthetic program was initiated, which led by 1995 to potent benzimidazole and quinazolinone inhibitors. These were much more effective than previously studied compounds and led, in collaboration with industrial partners (initially Agouron Pharmaceuticals), to the first-in-class clinical candidate by 2000 [**P3**-**P6**].

The primary contributions from Newcastle research was thus the design of new structural motifs for inhibition of PARP-1 and devising efficient synthetic routes to libraries of drug-like molecules needed to exemplify the concept. The discovery of potent benzimidazole inhibitors of PARP-1 enabled the support of a major pharmaceutical partner to be secured: initially Agouron Pharmaceuticals, world leaders in structure-based drug design (SBDD), which was an emerging technique in the 1990s. With the help of crystal structures of Newcastle inhibitors bound to PARP-1 protein, the number of molecules synthesised through the collaboration between the School of Chemistry and Agouron chemists led to the identification of the clinical candidate Rucaparib (AG014699, PF-01367338). This partnership was noteworthy because it came at a time when drug resistance modifiers and chemo-/radio-potentiators were considered to be of limited commercial value by the pharmaceutical sector. Our persistence and research therefore validated PARP as a viable target despite this prevailing attitude.

Preclinical research by the NICR validated the identified compounds as inhibitors of the target enzyme. Potentiation of the activity of alkylating agents (e.g. temozolomide) and topoisomerase I inhibitors (e.g. topotecan) was demonstrated in cell lines and also in xenograft models. The much wider clinical potential for PARP-1 inhibitors was shown by potentiation of ionising radiation and of cytotoxic drugs in a range of tumour types. After the clinical candidate Rucaparib had been identified, the Newcastle clinical team, with the support of Cancer Research UK (Drug

Development Office), designed and executed a first-in-human, first-in-class Phase I study of this compound in combination with temozolomide. This study was designed to provide both safety data and proof-of-mechanism of action in a surrogate tissue and also in tumour biopsies. It was one of the first Phase I studies to rely on a therapeutic (pharmacodynamic) endpoint rather than toxicity and pharmacokinetics alone. The Newcastle PARP-1 team was also closely involved in the preclinical research that first demonstrated synthetic lethality with PARP inhibitors in BRCA defective cell lines and proposed the first proof-of-principal Phase II study investigating this aspect.

In 2010, the PARP research team won Cancer Research UK's Translational cancer research prize which *"…recognises a team who have made a significant impact on the continuing effort to prevent, diagnose and cure cancer, and whose research is at the cutting edge of scientific novelty"* (http://science.cancerresearchuk.org/news/prize-winners-2010-announced). The intramural Newcastle PARP team that initiated the project embraced medicinal chemistry (Golding, Griffin), molecular, cell and *in vivo* pharmacology (*Curtin, 1989-date – Professor of Experimental Therapeutics; Newell, 1989-date – Professor of Cancer Therapeutics) and medical oncology (Calvert, 1990-2009 – Professor of Medical Oncology; Plummer - 2001-date – Professor of Experimental Cancer Medicine*).

3. References to the research

[**P1**] *R J Griffin, L C Pemberton, D Rhodes, C Bleasdale, K Bowman, A H Calvert, N J Curtin, B W Durkacz, D R Newell, J K Porteous, B T Golding, Novel potent inhibitors of the DNA repair enzyme poly(ADP-ribose)polymerase (PARP), *Anti-Cancer Drug Design*, 1995, 10, 507 - 514. *This paper was the first to describe benzimidazole carboxamides as potent PARP-1 inhibitors*.

[**P2**] R J Griffin, S Srinivasan, K Bowman, A H Calvert, N J Curtin, D R Newell, L C Pemberton, and B T Golding, Resistance-modifying agents. 5. Synthesis and biological properties of quinazolinone inhibitors of the DNA repair enzyme poly(ADP-ribose) polymerase (PARP), *J Med Chem*, 1998, 41, 5247-5256 (DOI: 10.1021/jm980273t).

[**P3**] *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).*This is the seminal paper on benzimidazole carboxamides as PARP-1 inhibitors showing that a substituted phenyl group at the 2-position of the imidazole ring gave enhanced potency. This study confirmed a predicted binding mode by X-ray analysis, in particular the importance of three hydrogen bonds from the carboxamide moiety.*

[**P4**] *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). *This paper was the first to show that tricylic systems related to the benzimidazole carboxamides gave improved properties as PARP-1 inhibitors and led the way to rucaparib.*

[**P5**] 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).

[**P6**] 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).

Selected grants

Cancer Research UK: Drug development Programme - 2007 – 2008: Awarded – £1,401,647; 2008 – 2009: Awarded - £986,663; 2009 – 2012: Awarded - £2,196,361; 2012 – 2015: Awarded - £738,433

4. Details of the impact

Overview

The primary impact of the Newcastle PARP project is the development of the anticancer drug Rucaparib. In addition, the Newcastle research has stimulated PARP research worldwide, which has led to further potent inhibitors. PARP research now embraces the global pharmaceutical industry (over 10 companies), with 33 cancer trials involving PARP inhibitors completed and an additional 52 trials currently open. Through these trials (50 Phase I, 33 Phase II and 2 Phase III) more than 7000 patients exhibiting 8 types of cancer have been treated with a PARP-1 inhibitor so far, including more than 200 patients who have received Rucaparib. The successful exploitation of PARP has established:

- *Structure-based drug design* (SBDD) as a major tool in cancer drug discovery.
- DNA damage repair as a viable target.

Beneficiaries

The research has had a significant impact on the global pharmaceutical industry, with companies such as AstraZeneca, Clovis, Sanofi-Aventis, Abbott, Merck, Biomarin, Eisai, Cephalon and Genentech having invested heavily in clinical trials and clinical PARP inhibitor programmes [**E1**]. Since the initial clinical trials in Newcastle in which patients were treated with a PARP inhibitor for the first time, there has been a twenty-fold increase in the commencement of trials testing PARP inhibitors [data extracted from **E1**].

Since the initial Phase 1 trial in 2003, more than 7000 cancer patients (approximately 750 of which have been recruited to more than one phase) have entered clinical trials involving PARP inhibitors [**E1**]. Five thousand six-hundred of these patients were enrolled since 2008. These trials include patients with ovarian cancer (incidence rate in the UK: 21 cases for every 100,000 women), breast cancer (157 new breast cancer cases for every 100,000 women and 1 for every 100,000 males in the UK) and prostate cancer (134 new prostate cancer cases for every 100,000 males in the UK; [**E2**]). Thirty-three cancer trials involving PARP inhibitors have been completed with an additional 52 trials currently open, totalling 50 Phase I, 33 Phase II and 2 Phase III trials [**E1**]. 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 [**E3**]. Therefore, an estimated $385 million US dollars has been invested into PARP inhibitor trials in the period 2008-2013.

In the earliest clinical trials of Rucaparib (2003 and 2005), although some patients had a life expectancy of only a few months, two treated in 2003 in the first clinical trial and five from a 2005 Phase II study with one exception are still alive and cancer-free [**E4**]. In one Phase II trial, treatment with the PARP inhibitor olaparib has significantly reduced the size of tumours in 38 % of breast cancer patients (9 of 24 patients) [**E5**]. Similarly, a Phase II trial showed that this drug was well tolerated in ovarian cancer patients with hereditary breast-ovarian cancer syndrome, with 33% (11 of 33 patients) showing reduced tumour size [**E6**].

As a consequence of Newcastle's PARP research, several other DNA damage and repair targets

are now being explored and Newcastle is involved in many of these, e.g. ATM, ATR, CHK1/2 and DNA PK.

Timeline for the Impact of the Newcastle PARP Inhibitor Programme

1995 – 2000 – Discovery of potent small molecule PARP inhibitors and initiation of a pre-clinical collaboration with Agouron Pharmaceuticals resulting in the identification of the first-in-class PARP inhibitor for clinical evaluation in cancer patients.

2000 – 2005 – Initiation of the first clinical trials of a PARP inhibitor in cancer in conjunction with Cancer Research UK and multiple UK clinical centres (Belfast, Oxford, Glasgow, Manchester, Birmingham), and Pfizer.

2005 – 2010 – Demonstration of the synthetic lethal interaction of PARP inhibition and BRCA deficiency, and the initiation of clinical trials in defined at risk patient groups in collaboration with Cancer Research UK and Pfizer.

2010 – Worldwide clinical trials of multiple PARP inhibitors in a range of cancers.

2010 – The Newcastle team were the recipients of the first Cancer Research UK Translational Research Award [**E7**].

2012 – Pfizer licence clinical development of Rucaparib to Clovis Oncology (Boulder, USA) [**E8**].

5. Sources to corroborate the impact

[**E1**] Search of clinical trials of PARP inhibitors indicating cancer disease types being studied and companies involved in the development of PARP inhibitors - www.clinicaltrials.gov. Search term 'PARP inhibitor', excluding withdrawn and terminated trials. For patient numbers, trials not yet recruiting were also excluded.

[**E2**] Search of prevalence rate for ovarian, breast and prostate cancers http://www.cancerresearchuk.org/cancer-info/cancerstats/types/

[**E3**] http://www.pharmalive.com/clinical-trial-costs-are-rising-rapidly (data sourced from "Oncology Clinical Trials: Drug Development Resources and Case Studies");

[**E4**] 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. (2008) Phase I study of the poly(ADP-ribose) polymerase inhibitor, AG014699, in combination with temozolomide in patients with advanced solid tumors. Clinical Cancer Research, **14**:7917-7923. DOI: 10.1158/1078-0432.CCR-08-1223.

[**E5**] 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)

[**E6**] 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)

[**E7**] Award to Newcastle of the inaugural Cancer Research UK Translational Research Team Prize in 2010 - http://science.cancerresearchuk.org/news/prize-winners-2010-announced.

[**E8**] http://www.clovisoncology.com/products-companion-diagnostics/rucaparib/