Institution: University of Cambridge

Unit of Assessment: 5

Title of case study: Revolutionising cancer therapy via the DNA-damage response

Period when the underpinning research was undertaken: 2000 - 2015

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:
Stephen P. Jackson	Frederick James Quick Professor of Biology	1991 to 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)

One in two people in the UK will develop cancer during their lifetime but currently only 50% of them are expected to survive for 10 years or more. Research at the University of Cambridge into DNA repair inhibitors led to a novel cancer therapy, Olaparib, that has been approved for ovarian, breast, pancreatic and prostate cancer treatment. Olaparib has been used to treat over 30,000 patients in 73 countries, reducing disease progression and death by up to 66%.

Olaparib was valued at USD17 billion in 2018 and in 2019 achieved an annual revenue of USD 1,198 million. So far, four companies, attracting significant investment, have been created to develop new drugs using this novel approach of DNA repair inhibitors to treat cancer, which has generated and supported over 70 jobs.

2. Underpinning research (indicative maximum 500 words)

It is estimated that 3-10% of diagnosed cancers are associated with an inherited faulty gene. Two genes that are known to increase cancer risk are BRCA1 and BRCA2. When functioning optimally, these genes protect us from cancer by correcting DNA damage during cell division. However, people who have a mutated version are at increased risk of developing cancer due to the reduced ability of their cells to repair DNA damage.

Professor Steve Jackson of the University of Cambridge has a long history in researching DNA repair and associated DNA damage responses (DDR). He is a world-class pioneer in DNA damage repair mechanisms and was one of the first to attempt to translate his basic research in this area to drug discovery, with the recognition that aberrant DNA damage repair pathways could be potential therapeutic targets.

Prof. Jackson and his team made many breakthroughs. They found a novel and potent inhibitor of a protein called ATM kinase, which controls the mobilisation and regulation of cellular responses to double-strand breaks, a specific form of DNA damage [R1], and identified the common motifs required to recruit the necessary proteins for DNA damage signalling and repair [R2]. They also demonstrated how the DDR is orchestrated by the protein RNF8 binding to MDC1, the DNA damage mediator protein, which enhances DNA-damage checkpoint events and promotes cell survival [R3].

In 2005, Prof. Jackson's research alongside scientists at his spin-out company, KuDOS Pharmaceuticals, and collaborators at Cancer Research UK, led to a publication showing

that BRCA1 and BRCA2 gene dysfunction unexpectedly sensitizes cells to the inhibition of PARP, a critical enzyme involved in DNA repair. This leads to chromosomal instability, cell cycle arrest and cell death. BRCA1 and BRCA2 deficient cancer cells were shown to be much more sensitive to PARP inhibition compared to cisplatin, a common chemotherapy medication that is used in cancer treatment to damage DNA [R4].

Prof. Jackson's research showed that PARP inhibitor treatment prevented the formation of tumours derived from BRCA2 deficient cells with no tumour formation after 100 days compared to 40% growth seen in the control group. These findings led the researchers to suggest a new approach for the treatment of patients with BRCA1 and BRCA2 associated cancers. Tumours in people with BRCA1 or BRCA2 mutations lack wild-type (non-mutated) BRCA1 or BRCA2 but their normal tissues retain a single wild-type copy of the relevant gene, meaning that normal tissues are not damaged by the treatment and are able to undertake standard DNA repair as usual [R4]. This pioneering study validated the concept of "synthetic lethality", wherein a cell with one mutated gene (such as BRCA1/2 in a cancer) is treated with an inhibitor of a second, compensatory gene product. This breakthrough from Prof. Jackson and colleagues at the University of Cambridge, and the associated drug discovery and development activities conducted with their collaborators, led to the first cancer therapy that specifically targets an inherited predisposition. This success resulted in the acquisition of Prof. Jackson's spin-out company, KuDOS, by AstraZeneca in 2005 for GBP 120,000,000 (The Guardian, AstraZeneca buys cancer specialist drug company, 24 Dec 2005).

In 2014, Prof. Jackson and colleagues built on their previous breakthrough by identifying several more enzymes linked to double-strand DNA repair that could be targeted for therapeutic targeting of cancers exhibiting high levels of DNA damage or that have underlying defects in DDR processes or chromatin components [R5]. This has now led on to further avenues of commercial and therapeutic development activity.

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

R1. Hickson I, Zhao Y, Richardson CJ, Green SJ, Martin NM, Orr AI, Reaper PM, **Jackson SP**, Curtin NJ, Smith GC. Identification and Characterization of a Novel and Specific Inhibitor of the Ataxia-Telangiectasia Mutated Kinase ATM. Cancer Res. 2004 64, 9152-9. DOI: 10.1158/0008-5472.CAN-04-2727.

R2. Falck J, Coates J, **Jackson SP**. Conserved modes of recruitment of ATM, ATR and DNA-PKcs to sites of DNA damage. Nature 2005 434, 605-611. DOI: 10.1038/nature03442.

R3. Kolas NK, Chapman JR, Nakada S, Ylanko J, Chahwan R, Sweeney FD, Panier S, Mendez M, Wildenhain J, Thomson TM, Pelletier L, **Jackson SP,** Durocher D. Orchestration of the DNA-damage response by the RNF8 ubiquitin ligase. Science 2007 318, 1637-1640. DOI: 10.1126/science.1150034.

R4. Farmer H, McCabe N, Lord CJ, Tutt ANJ, Johnson DA, Richardson TB, Santorosa M, Dillon K J, Hickson I, Knights C, Martin NMB, **Jackson SP**, Smith GCM, Ashworth A. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature 2005 434, 917-921.DOI: 10.1038/nature03445.

R5. Nishi R, Wijnhoven P, le Sage C, Tjeertes J, Galanty Y, Forment JV, Clague MJ, Urbé S, **Jackson SP**. Systematic characterization of deubiquitylating enzymes for roles in maintaining genome integrity. Nat Cell Biol. 2014 Oct;16(10):1016-26, 1-8. DOI: 10.1038/ncb3028.

All research outputs have been published in peer-review journals.

Competitive funding received

- 2000 – 2004 CRUK studentship C6/A2761 (2000-2004), GBP88,000 [RG unknown]
- 2000 – 2005 The detection, signalling and repair of DNA damage, CRUK programme grant C6/A1672 GBP1,650,000 [RG 31627]
- 2005 – 2010 Cellular response to DNA damage, CRUK programme grant C6/A5290, GBP2,863,947 [RG 40339]
- 2010 – 2015 Cellular response to DNA damage, CRUK programme grant C6/11224, GBP3,731,158 [RG 60825]
- 2011 – 2016 DNA-Damage responses: dynamics, regulation, mechanisms and screens, ERC Advanced Researcher Grant, GA 268536, GBP2,216,676 [RG 59649]
- 2012 – 2015 Identifying and characterising deubiquitylating enzymes that control cellular response to DNA double-strand breaks, CRUK Project grant C6/A14831, GBP182,533 [RG 64601]

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

Human health and quality of life

Prof. Jackson's discovery that DNA repair pathways could be targeted in cancer therapy led to the production of Olaparib, the world's first marketed DNA-repair enzyme inhibitor. Olaparib is the first drug to exploit the principle of 'synthetic lethality', and the first cancer drug to target an inherited predisposition [E1].

Since 2014, Olaparib has become an increasingly important drug for cancer treatment, having been approved for use in 73 countries as treatment for four types of cancer (Table 1). Furthermore, clinical trials are underway to assess its suitability for other cancers, where it has, for example, been found to give increased survival benefit against head and neck cancer, with a 72% two-year survival [E2]. Due to worldwide approval (see Table 1, below), to date Olaparib has been used to treat over 30,000 patients, including 15,000 in 2019 [E3]. AstraZeneca estimates that 300,000 patients' lives will have been significantly improved by the use of Olaparib by 2025 [E1].

A senior professor from the Institute of Cancer Research, who played a pivotal part in the clinical trials for Olaparib, says, "Prof. Jackson's research and subsequent therapeutic development has hugely influenced anti-cancer treatment. It has paved the way for targeting the DNA damage response as a means to treat cancer, extending and improving the lives of thousands of patients worldwide" [E1]. Sandy Tansley, who took Olaparib for ovarian cancer after chemotherapy, said that "Steve Jackson has saved my life... I am just the most lucky person in the world" [E4]. Florence Wilks, who has been taking Olaparib for over two years after four rounds of chemotherapy and two rounds of surgery for ovarian cancer, said "it's a gamechanger in terms of treatment because it's an easy drug to take in comparison with chemo. Without Olaparib, I basically wouldn't be here. My children would not have a mother, which I can't even bear to think about. When I look back to that fourth lot of chemo when I said, "That's it, I'm not doing it anymore - I can't do it anymore", and now, more than two years in, I live a pretty normal life. It's hard to describe how wonderful that is" [E4].

Olaparib has a wide range of proven successful outcomes. It has been hailed as bringing the goal of long-term remission and cure closer for certain ovarian cancers [E3] and has almost doubled life expectancy without disease progression for patients with BRCA mutated metastatic pancreatic cancer [E3]. The most recent approval for Olaparib by the FDA and EMA is for the treatment of homologous recombination repair (HRR) gene mutated prostate cancer. Prostate cancer is the second most common cancer in men, of which 20 – 30% are HRR gene mutated, and five-year survival is low. Clinical trials show that Olaparib can reduce the risk of disease progression and death by HRR gene mutated prostate cancer by 51% and by 66% in individuals with BRCA1/2 and ATM gene mutations [E5].

Table 1. Countries with Olaparib approval by cancer type [E3; E6; E7; E8]

Type of cancer	Countries where approved (and year of approval)
Platinum sensitive relapsed ovarian, fallopian tube and primary peritoneal cancer	73 countries including the EU (2018)
1st line maintenance treatment of BRCA mutated advanced ovarian, fallopian tube and primary peritoneal cancer	US (2014), EU (2019), Japan (2019), China (2019) + several others
Germline BRCAm, HER2-negative, metastatic breast cancer	58 countries including the US (2018), EU (2019) and Japan
Locally advanced breast cancer	EU countries (2019)
1st line maintenance treatment for germline BRCA mutated metastatic pancreatic cancer	US (2019), EU (2020)
HRR gene mutated metastatic castration-resistant prostate cancer	US (2020), EU (2020)

Economy

Investment and revenue

With clinical trials continuing to show Olaparib as a powerful therapy for various cancer types, its value and revenue continue to grow. In 2018, Olaparib was valued at USD17 billion [E9] and in 2019, the drug's revenue reached USD 1,198 million [E3]. Companies that are using the same approach of DNA repair inhibition developed by Prof. Jackson have attracted significant investment, highlighting demand for this type of therapy. For example, Mission Therapeutics has attracted venture capital funding worth GBP87 million (USD130 million), Artios has raised GBP 90 million [E1] and Adrestia has received substantial seed funding (undisclosed amount).

Companies created

The success of Olaparib has paved the way for the establishment of various other programmes in pharma companies such as AstraZeneca, based on Prof. Jackson's discoveries [E1]. It has also paved the way for the establishment of various biotech companies since 2014, in the UK and elsewhere, that are targeting the DNA damage response. This includes Artios Pharma Ltd (2015), Ideya Biosciences (2015), Repare Therapeutics (2016) and Tango Therapeutics (2017).

Alongside these new companies is Adrestia (co-founded by Prof. Jackson in 2018), which builds on the breakthrough discoveries in DDR and synthetic lethality to apply the concept of synthetic viability as a way of identifying drug targets for inherited rare diseases caused by single gene mutations. As well as Adrestia, Mission Therapeutics (founded 2011 by Jackson) is a world leader in deubiquitylating enzyme drug discovery. Mission Therapeutics announced a major collaboration with AbbVie in 2018 for research and pre-clinical development of specific DNA repair inhibitors for the treatment of Alzheimer's disease and Parkinson's disease [E1]. In 2020, Mission Therapeutics announced they had raised GBP12 million in equity investment led by collaborator Pfizer [E10].

Job creation

Prof. Jackson's discovery of DNA repair inhibitors and their use in cancer therapy has led to the creation of many jobs across several UK-based companies including the following (at end 2019):

- Mission Therapeutics now has more than 45 employees in roles including drug metabolism and pharmacokinetics, preclinical project management, and clinical development [E11, page 15 (numbered 14 in document)].
- Artios Pharma Ltd has 31 employees in research and development and six in administration and operations [E11]. The company aims to develop breakthrough

cancer treatments that target DDR pathways to specifically destroy certain cancers that are difficult to treat.
- Adrestia has three full time staff members [E11].

The significance of Prof. Jackson's work on Olaparib has been recognised by numerous awards and accolades, which has been described by the Royal Society as having "reached blockbuster status for the treatment of ovarian and breast cancers". The Royal Society in 2020 awarded Jackson with the Mullard Award in recognition of his contribution to national prosperity [E12].

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

Evidence list

E1. Combined testimonials from the Institute of Cancer Research, AstraZeneca, Artios Pharma and Mission Therapeutics
E2. Clinical trial information publication and clinical trial study details
E3. AstraZeneca annual report 2019; pages numbered 55-56 (57-58 of document) detail annual revenue for Olaparib (Lynparza)
E4. Patient testimonial from Ovarian Cancer Action UK's YouTube site
E5. AstraZeneca press release Olaparib approved for use in metastatic castration resistant prostate cancer
E6. NICE guidelines combined for ovarian, breast and pancreatic cancer
E7. FDA approval combined for ovarian, breast, pancreatic and prostate cancer
E8. EMA approval combined for ovarian, breast and pancreatic cancer
E9. Article on Merck and AstraZeneca collaboration detailing Merck paid USD 8.5 billion for a 50% share
E10. Press release from Mission Therapeutics on Pfizer collaboration
E11 Combined Artios (page 15) and Adrestia (page 22) financial statements detailing number of employees end of 2019
E12. Royal Society recognition