Institution: University of Cambridge

Unit of Assessment: UoA5

Title of case study: The DNA damage response in human biology and disease

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

Research by Professor Steve Jackson led to the discovery of synthetic lethality as a means of selectively targeting cancer cells, and to Jackson founding KuDOS Pharmaceuticals to translate this research into therapies. This novel approach has changed the way pharmaceutical companies develop cancer therapeutics and has led to several drugs reaching pre-clinical and clinical development. The most advanced of these (olaparib, a PARP inhibitor originally developed at KuDOS and acquired by Astra Zeneca) is now entering Phase 3 trials and registration in Europe. In 2011, Jackson founded *MISSION* Therapeutics Ltd, to extend the synthetic lethality concept into targeting deubiquitylating enzymes to selectively kill tumour cells.

2. Underpinning research (indicative maximum 500 words)

Professor Steve Jackson joined the University of Cambridge (Wellcome Trust/Cancer Research UK Gurdon Institute) in 1991, becoming the Quick Professor of Biology. His major research focus has been on cellular responses to DNA damage. He has identified many key DNA damage response (DDR) proteins, and demonstrated how the DDR impinges on telomere maintenance and chromatin structure, and helped to reveal that DDR defects lead to genome instability, immune deficiency, neuro-degeneration, and cancer.

From 1993, Jackson and colleagues (PDRA; Graeme Smith 1994-1999, research technicians; Kathy Hartley 1991-1994, Rebecca Izzard 1996-1999) continued a body of research on DNA-dependent protein kinase (DNA-PK), having recently shown that DNA ends and Ku antigen binding were required for its mechanism of action. Importantly, they demonstrated, by cell culture- and biochemistry-based methods, that DNA-PK (involved in double strand break repair and V(D)J recombination) comprised a DNA-targeting component (Ku), and a catalytic subunit (DNA-PKcs) that was related to the phosphatidylinositol (PI) 3-kinases. Strikingly, Jackson found that DNA-PKcs is similar to kinases involved in cell cycle control, DNA damage responses and DNA repair; mutations of which (e.g. the ataxia-telangiectasia gene ATM) lead to genomic instability and predisposition to cancer [Hartley 1995, Cell]. Recognising the clinical significance of this, Jackson sought to develop medium/high throughput drug screening methods for compounds targeting DDR pathways. In 1997 Jackson filed 4 patents on therapeutic and diagnostic methods relating to his work (patent families; WO9830903, WO9830902, WO9904266, WO9931234), covering Europe, Japan, Australia, Canada and in 3 cases the US. Based on these and his overall research, he founded KuDOS Pharmaceuticals Ltd, in 1997 (with support from the University and from Cancer Research UK), to translate research from the Jackson lab into novel cancer therapies.

In 1999 Jackson's group, studied the effects of the known PI3- / PI4-kinase inhibitors; wortmannin, LY294002 and quercetin on DNA-PK activity in human lymphoblastoid and human glioma cells. Whilst LY294002 and quercetin inhibited DNA-PK in a competitive manner, inhibition by wortmannin was non-competitive with binding to the DNA-PKcs being independent of Ku- or DNA, but sensitive to ATP. Although the study demonstrated that the profile of these inhibitors was broader than previously expected, it raised the possibility that derivatives of these compounds could serve as the basis of more selective inhibitors for DNA-PKcs. Given that wortmannin and LY294002 were known to radiosensitize mammalian cells, in culture, Jackson recognised that such agents could have therapeutic potential by increasing the efficacy of cancer chemotherapy and radiotherapy [Izzard 1999 Cancer Research]. Further research led by Jackson, in collaboration

with Byron Hann (University of Dundee), led to the identification of a novel DNA-activated protein kinase; ataxia-telangiectasia related protein "ATR", which phosphorylates the tumour suppressor protein p53 and acts in a manner distinct from DNA-PK [Lakin 1999 Oncogene]. The three PI 3 kinase-related protein kinases (PIKKs); ATM, ATR and DNA-PKcs were then studied further in recombinant cells, and by a combination of immunohistochemistry and immunoprecipitation, shown to share the same mode of recruitment to sites of DNA damage [Falck 2005 Nature].

Since mutation of ATM (as in the autosomal recessive disorder ataxia-telangiectasia) causes hypersensitivity to ionizing radiation, and damage after DNA double strand breaks, Jackson sought to determine whether inhibition of this kinase would also lead to radio- and chemosensitization. In 2004, together with researchers now based at KuDOS Pharmaceuticals Ltd, he led a study to screen a library of small molecules designed to inhibit PIKKs, and identified a novel inhibitor, selective against ATM; Ku55933 [Hickson 2004, Cancer Res]. Exposure of cells to this compound indeed resulted in sensitization to the cytotoxic effects of ionizing radiation and to agents known to induce DNA double strand breaks.

The method of targeting defects in the DNA repair pathway as a therapeutic strategy for cancer was developed further in a pioneering study published in Nature in 2005. Here, Jackson, together with researchers at KuDOS Pharmaceuticals and Cancer Research UK, demonstrated that inhibition of poly(ADP-ribose) polymerase (PARP), a key enzyme in the repair of DNA single strand breaks, was lethal to cells already compromised in DDR pathways due to a mutation of BRCA1/2; (each key to double strand break repair, mutations of which predispose to several cancers). This pioneering study introduced the concept of "synthetic lethality", wherein two genes that are not lethal when mutated individually (or the gene products inhibited individually) are lethal when the two genes are mutated within the same cell, or translating to a clinical setting; a cell with one mutated gene (such as BRCA in cancer) has the second gene product (a kinase of the DDR pathway) artificially inhibited (here with the PARP inhibitor KU0058684 [Farmer 2005, Nature]. Jackson's recent research has shown how protein ubiquitylation and sumoylation control cancer-relevant DNA repair processes [e.g. Kolas et al, Science 2007], leading him to establish *MISSION* Therapeutics, a company that is developing small-molecule inhibitors of ubiquitylation and deubiquitylation to target new synthetic-lethality opportunities in cancer.

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

1. Hartley K, Gell D, Smith GCM, Zhang H, Divecha N, Connelly MA, Admon A, Lees-Miller SP, Anderson CW and Jackson SP. (1995) DNA-dependent protein kinase catalytic subunit: a relative of phosphatidylinositol 3-kinase and the ataxia telangiectasia gene product. **Cell** 82, 849-856.
2. Izzard, R. A., Jackson, S. P. and Smith, G. C. M. (1999). Competitive and noncompetitive inhibition of the DNA-dependent protein kinase. **Cancer Research** 59, 2581-2586.
3. Lakin ND, Hann BC, Jackson SP. (1999). The ataxia-telangiectasia related protein ATR mediates DNA-dependent phosphorylation of p53. **Oncogene** 18, 3989-3995.
4. Falck J, Coates J, Jackson SP (2005) Conserved modes of recruitment of ATM, ATR and DNA-PKcs to sites of DNA damage. **Nature** 434, 605-611.
5. Hickson I, Zhao Y, Richardson CJ, Green SJ, Martin NM, Orr AI, Reaper PM, Jackson SP, Curtin NJ, Smith GC. (2004) Identification and Characterization of a Novel and Specific Inhibitor of the Ataxia-Telangiectasia Mutated Kinase ATM. **Cancer Res.** 64, 9152-9.
6. 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 (2005) Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. **Nature** 434, 917-921.
7. Kolas, N.K., Chapman, J.R., Nakada, S., Ylanko, J., Chahwan, R., Sweeney, F.D., Panier, S., Mendez, M., Wildenhain, J., Thomson, T.M., Pelletier, L., Jackson, S.P. and Durocher, D. (2007). Orchestration of the DNA-damage response by the RNF8 ubiquitin ligase. **Science** 318, 1637-1640.

Key research grants 1993-2010 (Jackson as PI unless otherwise indicated):

Cancer Research Campaign; 1991-1996; £532,231 and 1996-2001; £884,160.
Cancer Research UK. 2000-2005; £1,650,000 and 2005-2010; £2,863,947.
EU Framework Programme 6. 2005-2009, 15 participants; grant to Jackson lab: £707,857.
EU Framework Programme 7. 2008-2010, 11 participants; grant to Jackson lab: £139,000.
MRC Link Applied Genomics Grant. 2003-2005; grant to Jackson lab: £179,889.

Recipient of the Biochemical Society 2008 GlaxoSmithKline Award and of BBSRC Innovator of the year 2009: for work that led to establishment of KuDOS and its eventual acquisition by AZ

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

Research by Jackson and colleagues led to the development of novel therapies and approaches to treatment for cancer and to the spin-out company KuDOS Pharmaceuticals, acquired by AstraZeneca in 2010. This has subsequently had a large impact on health and commerce in several ways;

Impact on Health; novel therapeutics

1) PARP inhibitors; Olaparib, originally developed by KuDOS Pharmaceuticals Ltd. (Ku-0059436), since acquired by AstraZeneca (AZD2281) has been used in over 30 Phase 1/2 clinical trials [ref 1] (either on-going or completed since 2008, over 20 of which started after 2008). These have targeted a range of cancers including; breast, ovarian, colorectal, lung, pancreatic and gastric cancer. Most recently (June 2013) olaparib was approved for a Phase 3 clinical trial (NCT01844986) for the management of BRCA-mutated ovarian cancer [ref 2].

2) m-TOR inhibitors; Jackson's work screening small libraries of compounds targeting various related kinases; m-TOR, ATM and DNA-PK, directly led to KuDOS Pharmaceuticals and AstraZeneca developing two m-TOR inhibitors as cancer therapeutics; AZD8055 (now in Phase 1 clinical trials; NCT00731263, NCT00999882, NCT00973076 sponsored by AZ and NCT01316809 sponsored by NCI) [ref 3] and AZD2014 (which has reached Phase 1 (NCT01026402, NCT01597388) and Phase 2 (NCT01793636) trials) [ref 4].

3) AstraZeneca also have an ATR inhibitor; AZ20 in pre-clinical development. This has anti-tumour activity in vivo [ref 5] and is expected to enter Phase 1 clinical trials in the near future.

Impact on Commerce; new business/ spin-out company established

KuDOS Pharmaceuticals was founded by Jackson in 1997 (seed-funded), received its first venture capital funding in 1999 and was acquired by AstraZeneca for $210 million in 2006. It remained semi-autonomous until 2010 when its programmes were transferred entirely into AstraZeneca [Ref 6]. At the time of acquisition, KuDOS had expanded to 75 employees. *MISSION* Therapeutics Ltd (a private drug discovery company in Cambridge) was founded by Jackson in 2011 in order to develop small molecule drugs that target deubiquitylating enzymes (DUBs) involved in the DNA damage response, with the aim of inducing synthetic lethality, to selectively kill specific tumour cells. In 2011 the company raised £6 million in Series A funding from a strong venture capital syndicate led by Sofinnova Partners, and comprising Imperial Innovations, SR One and Roche Venture Fund. *MISSION* was recently (February 2013) granted a Biomedical Catalyst Feasibility Award by the Technology Strategy Board (£144,000) to support the identification of DUBs required for the survival of drug-resistant ovarian cancers. *MISSION* currently has 19 employees and funds over 30 FTE posts at various clinical research organisations in the UK and beyond.

Impact on Commerce; new products commercialised

A number of compounds developed by KuDOS as a result of Jackson's work have been sold by agreement (initial agreement with either KuDOS or AstraZeneca) for research purposes and

continue to be sold and / distributed by Tocris Cookson (i.e.; the m-Tor inhibitor Ku-0063794, the ATM inhibitors Ku-55933 and Ku-60019 and the selective DNA-PK inhibitors Nu-7441 and NU7026 developed at Newcastle University in collaboration with KuDOS.) [Ref 7]. Ku-0063794 is also widely distributed by several providers of compounds for medical research including; Sigma-Aldrich, Caymen Chemicals, Stemgent, Stratech, Selleckchem.

Impact on Commerce; a new approach has been adopted by the pharmaceutical industry

Jackson's pioneering approach of "synthetic lethality", as a means of specifically targeting tumour cells, was recognised by researchers in the field as leading cancer therapy in a "new direction". Alongside the publication of the Phase 1 study (NCT00516373) of olaparib in patients with BRCA mutations (Fong et al. 2009, NEJM; 3 KuDOS-based co-authors), an accompanying article (Inglehart and Silver 2009, NEJM) highlighted the importance of this early phase trial, based on its novel approach [Ref 8]. The approach of synthetic lethality and targeting DDR pathways in general, has been widely adopted by pharmaceutical companies seeking to develop their own PARP, DNA-PK, ATM and ATR inhibitors (for recent review with examples of compounds in pre-clinical and clinical development see Ref 9), which now include a number of dual-specificity inhibitors that target several aspects of the DNA repair pathway. For example, Celgene Corporation have developed a dual DNA-PK and TOR inhibitor; CC-115 that is about to enter Phase 1 clinical trials (NCT01353625) [Ref 10]. Astra Zeneca have invested in excess of £50M in the area of DNA repair since the acquisition of KuDOS [Ref 11].

Impact on public awareness

Steve Jackson has engaged with the charity Cancer Research UK to increase public understanding of the process of DNA repair and its links with cancer and the progress being made in his lab (for example see interview in 2011; Ref 12).

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

1. http://clinicaltrials.gov/ct2/results?term=AZD2281&Search=Search
2. http://clinicaltrials.gov/ct2/show/NCT01844986
3. http://clinicaltrials.gov/ct2/results?term=AZD8055&Search=Search
4. http://clinicaltrials.gov/ct2/results?term=AZD2014&Search=Search
5. http://pubs.acs.org/doi/pdf/10.1021/jm301859s
6. http://www.bloomberg.com/apps/news?pid=newsarchive&sid=aIv205k6elRw&refer=uk
7. http://www.tocris.com/
8. http://www.nejm.org/doi/full/10.1056/NEJMe0903044
9. http://www.smw.ch/content/smw-2013-13837/
10. http://clinicaltrials.gov/ct2/results?term=NCT01353625&Search=Search
11. Letter from Executive Vice President, Innovative Medicines and Early Development, AstraZeneca R& D, Macclesfield
12. http://myprojects.cancerresearchuk.org/projects/cambridge-research