Institution: Cardiff University

Unit of Assessment: Clinical Medicine (1)

Title of case study: Genetic profiling establishes mTOR inhibitors as first line therapy for tuberous sclerosis-associated kidney disease

Period when the underpinning research was undertaken: 2008-2013

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:
Julian Sampson	Clinical Professor	01/11/1998-present
Ming Hong Shen	Senior Research Fellow	1/06/2007-30/04/2020

Period when the claimed impact occurred: 2013-2020

Is this case study continued from a case study submitted in 2014? No

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

Benign tumours of the kidney affect patients with incurable tuberous sclerosis complex (TSC). Before the Cardiff research, all treatments carried risks of immediate complications and permanent renal damage. Cardiff researchers showed that disease-causing genetic mutations in TSC resulted in altered mTOR signalling. Subsequent clinical studies identified mTOR inhibitors as novel therapies for TSC, shrinking renal tumour growth and alleviating wider disease manifestations. This research led to the worldwide approval of mTOR inhibitors as a frontline therapy for the clinical management of TSC.

2. Underpinning research (indicative maximum 500 words)

Tuberous sclerosis complex (TSC) affects around 1 in 10,000 people. It is characterised by the growth of benign tumours, most commonly in the kidneys, brain and lungs. Although the tumours are generally non-malignant, life-threatening co-morbidities mean that renal defects due to angiomyolipomas (kidney tumours) are the leading cause of adult death from TSC. Other common symptoms of TSC include skin abnormalities, epilepsy, behavioural problems and learning difficulties.

Researchers at Cardiff University have a well-established track-record of research into the causes and management of TSC. Prior to 2000, the Cardiff research team led the research consortium that identified the *TSC2* gene and were members of the consortium that identified the *TSC1* gene. These studies also characterised the disease-causing genetic mutations in *TSC1* and *TSC2.* The normal functions of *TSC1* and *TSC2* are to inhibit growth signals via the mammalian target-of-rapamycin (mTOR) pathway; these studies showed that mutation of either *TSC1* or *TSC2* causes the uncontrolled cell growth characteristic of TSC.

2.1 Targeting the mTOR pathway to overcome TSC1/2 mutations

The discovery of the link between *TSC1/2*, mTOR signalling and tumour growth in TSC presented the possibility that TSC tumours could be treated with the existing drug rapamycin, rather than through surgery. Cardiff researchers carried out studies to explore the broader implications of mTOR inhibition in transgenic $Tsc^{+/-}$ mouse models of TSC, using both rapamycin (sirolimus) and related rapalogues (everolimus). They showed that:

- Contrary to the expectation of feedback inhibition via Akt signalling, both mTOR and Akt were up-regulated in tumour cells from a $Tsc2^{+/-}$ mouse and sirolimus was highly effective in downregulating both Akt and mTOR and preventing tumour growth **[3.1, G3.1]**.
- The addition of sorafenib, an established renal cell carcinoma drug, to everolimus was promising for treating larger tumours **[3.2, G3.2, G3.3]**.
- The joint inhibition of both mTOR and phosphatidylinositol-3-kinase with the novel compound GSK2126458 induced greater apoptosis in solid tumours, but sirolimus

alone had a stronger inhibitory effect on the mTOR pathway in renal tumours **[3.3, G3.2, G3.3]**.

In summary, the Cardiff team demonstrated direct mTOR inhibition to be a robust approach for treatment. Furthermore, although drugs targeting additional proteins in the mTOR pathway showed some promise, mTOR inhibition was the most promising standalone treatment.

2.2 TESSTAL trial

The Cardiff team led an investigator-initiated open label phase 2b clinical trial, TESSTAL, designed to assess the efficacy and safety of oral sirolimus in treating TSC and lymphangioleiomyomatosis patients with renal angiomyolipomas (lymphangioleiomyomatosis is a lung disease affecting women caused by *TSC2* mutations). The primary outcome measure was reduction is size of angiomyolipomas **[3.4, 3.5, G3.4, G3.5].** The trial found that:

- Across 2 years of treatment, renal angiomyolipoma burden was reduced in all patients.
- 50% of patients had responses that met RECIST criteria (i.e., 30% reduction in angiomyolipoma maximum diameter).
- Of 23 renal angiomyolipomas, 21 were smaller after 2 years, 2 were unchanged;
- Sustained treatment was necessary to maintain reductions in tumour size. This was reinforced by the findings of a parallel US open label trial led by the Cincinnati Children's Hospital, which treated patients with sirolimus for only 12 months, and found that their angiomyolipomas increased in size in the 12 months after treatment ended (Bissler et al, 2008, NEJM DOI: 10.1056/NEJMoa063564).

2.3 Establishing the use of mTOR inhibitors in patients with different TSC1/TSC2 mutations

TSC patients may have a range of genotypes, with a variety of mutations in either *TSC1* or *TSC2*. Prior to Cardiff research, it was not known whether patient responses to treatment with mTOR inhibitors depended on mutation. In a joint study between Cardiff and their international collaborators, including Bissler from Cincinnati, everolimus treatment in TSC patients with varying genotypes was assessed. Notably, no correlation was seen between type of mutation and response to everolimus **[3.6, G3.6]**. Based on these findings, the researchers concluded that mTOR inhibitor therapy could be used across all TSC patients, regardless of their underlying genetics.

The Cardiff team's rigorous investigation of mTOR signalling in the pathology and treatment of TSC provided the evidence base for the successful use of mTOR inhibitors in the clinical management of the disease.

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

[3.1] Yang J, Kalogerou M, Samsel PA, Zhang Y, Griffiths DF, Gallacher J, **Sampson JR*, Shen MH.*** Renal tumours in a $Tsc2^{+/-}$ mouse model do not show feedback inhibition of Akt and are effectively prevented by rapamycin. Oncogene. 2015 February 12;34(7):922-31. doi: 10.1038/onc.2014.17

[3.2] Yang J, Samsel PA, Narov K, Jones A, Gallacher D, Gallacher J, **Sampson JR, Shen MH.** Combination of everolimus with sorafenib for solid renal tumors in $Tsc2^{+/-}$ mice is superior to everolimus alone. Neoplasia. 2017 February 19(2):112-120. doi: 10.1016/j.neo.2016.12.008

[3.3] Narov K, Yang J, Samsel P, Jones A, **Sampson JR, Shen MH.** The dual PI3K/mTOR inhibitor GSK2126458 is effective for treating solid renal tumours in $Tsc2^{+/-}$ mice through suppression of cell proliferation and induction of apoptosis. Oncotarget. 2017 April 19;8(35):58504-58512

[3.4] Davies DM, Johnson SR, Tattersfield AE, Kingswood JC, Cox JA, McCartney DL, Doyle T, Elmslie F, Saggar A, deVries PJ, **Sampson JR**. Sirolimus therapy in tuberous sclerosis or

sporadic lymphangioleiomyomatosis. New England Journal of Medicine. 2008 January 358(2): 200-203. doi: 10.1056/NEJMc072500

[3.5] Davies DM, de Vries PJ, Johnson SR, McCartney DL, Cox JA, Serra AL, Watson PC, Howe CJ, Doyle T, Pointon K, Cross JJ, Tattersfield AE, Kingswood JC**, Sampson JR**. Sirolimus therapy for angiomyolipoma in tuberous sclerosis and sporadic lymphangioleiomyomatosis: a phase 2 trial. Clin Cancer Res. 2011 June 15;17(12):4071-81. doi: 10.1158/1078-0432.CCR-11-0445

[3.6] Kwiatkowski DJ, Palmer MR, Jozwiak S, Bissler J, Franz D, Segal S, Chen D, **Sampson JR**. Response to everolimus is seen in TSC-associated SEGAs and angiomyolipomas independent of mutation type and site in TSC1 and TSC2. Eur J Hum Genet. 2015 December 23(12):1665-72

Selected grants:

[G3.1] Welsh Government WORDSCH award Wales Gene Park 500584 £4,548,125 01/04/2010-01/06/2015 Funded research reported in papers

[G3.2] Welsh Government HCRW award Wales Gene Park 508339 £2,500,000 01/04/2015-31/03/2018 Funded research reported in papers

[G3.3] Tuberous Sclerosis Association 2013-P02 Prevention of renal lesions by tuning mTOR signalling in a model of tuberous sclerosis £176,804 01/03/2014-31/12/2018 Funded research reported in papers

[G3.4] Welsh Government Wales Gene Park RCUF064 £2,634,838 01/04/2005-31/03/2010. Funded research reported in papers

[G3.5] Tuberous Sclerosis Association The efficacy and safety of rapamycin (Sirolimus/Rapamune) for treatment of angiomyoliomas in tuberous sclerosis complex and sporadic lymphangioleiomyomatoisis 05/01 £101,361 01/07/2005-31/11/2010 Funded research reported in papers

[G3.6] Association for International Cancer Research Identifying and characterising novel mammalian target of rapamycin (mTOR) substrates 06-914/915 £735,418 01/02/2007-28/02/2013

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

The Cardiff team's research on the molecular mechanisms underlying tumour growth in TSC patients, and the effectiveness of mTOR inhibitors to reduce tumour growth, resulted in changes to international disease management guidelines. Their work also provided the basis for a successful lobbying campaign by the UK charity, the Tuberous Sclerosis Association, for the NHS to commission mTOR inhibitors for TSC patients.

4.1 International guidelines

Cardiff research contributed to the 2013 publication of Surveillance and Management Clinical Guidelines, developed from the 2012 International Tuberous Sclerosis Complex Consensus Conference. The new international guidelines recommended mTOR inhibitors as first line treatment for renal angiomyolipomas and are considered the international standard for clinical management of TSC **[5.1]**. Referring to the Cardiff research paper **[3.5]**, the guidance states that: *"For asymptomatic, growing angiomyolipoma measuring larger than 3 cm in diameter, treatment with an mTOR inhibitor is the recommended first-line therapy*" **[5.1**, table 3, p.19**]**.

The Tuberous Sclerosis Alliance (TS Alliance) is a US-based charity which commands a multi-million-dollar research budget and aims to improve treatment options, access to care and awareness of TSC both in the US and internationally. The TS Alliance sponsored the development and dissemination of these guidelines, and in describing Cardiff's role, notes: "*The evidence provided by Cardiff University's research was an essential factor in the process leading to the change in policy and clinical practice that has now become established globally*" **[5.2].** In 2017, the TS Alliance awarded Sampson their highest honour, the Manual R. Gomez Award, in recognition of Cardiff's impactful research **[5.2]**.

4.2 NHS clinical commissioning policy statements on everolimus

Prof Bissler summarised the importance of Cardiff research in the approval of mTOR inhibitors, including everolimus, as a treatment strategy for TSC: *''Following [Cardiff] work identifying and characterizing the TSC2 gene my group in Cincinnati and yours in Cardiff undertook phase IIb studies to establish initial evidence for safety and efficacy of sirolimus treatment for this important manifestation of TSC **[3.5]**…These foundational studies lead to our registration trial using everolimus, and finally the approval of such mTORC1 inhibitor therapy"* **[5.3, 5.4]**.

In 2015, NHS Wales was the first UK health service to commission mTOR inhibitors for the treatment of angiomyolipomas in TSC, prior to appraisal of everolimus by NICE **[5.5]**. This included a 2-year deal with Novartis, who agreed to invest £1.3M to run an observational study of patients being treated with everolimus, as part of plans for future appraisal of the treatment **[5.5]**.

Despite the commissioning of mTOR inhibitors for Welsh patients, access to treatment in England required individual patient funding requests (IPFR) to access the drug. The Tuberous Sclerosis Association, a UK charity representing TSC patients, discovered that IPFRs for mTOR inhibitor treatment were rarely successful, with fewer than 5 approved in 2014-2015 **[5.6]**. Following the success of trials, including Cardiff's TESSTAL trial, the Tuberous Sclerosis Association lobbied and campaigned for mTOR inhibitors to be commissioned by NHS England for the treatment of TSC patients in England **[5.6]**. As a result, in 2016 NHS England: *"reviewed the evidence and concluded that it is sufficient to enable everolimus (Votubia®) to be routinely commissioned and therefore available to children from three years of age and adults with TSC-associated AMLs*" **[5.7]**. The evidence described in the commissioning statement included the Cardiff-led TESSTAL trial **[3.5, 5.7]**.

4.3 UK guidelines for management and surveillance of TSC

Sampson was an author of new 2019 UK Guidelines for Management and Surveillance of TSC, which were developed through repeated online surveys of 86 UK clinicians and researchers, as well as consultation with the Tuberous Sclerosis Association. The two surveys constituted a Delphi process, by which a consensus was reached **[5.8]**. Cardiff research **[3.4, 3.5]** underpins these UK guidelines, which state that "*There was a consensus that growing AMLs measuring ≥3cm in diameter should be treated with mTOR inhibitors*". These were the first UK guidelines to be produced on management of TSC, with the importance of these guidelines noted by the Tuberous Sclerosis Association on their website: "*Publication of the UK TSC clinical guidelines was a defining moment in the diagnosis, treatment and management of people living with TSC, with the guidelines helping to drive improvements in the consistency and quality of care that people with TSC receive from the NHS*" **[5.9]**.

4.4 Improved patient outcomes

In addition to Cardiff's trials into mTOR inhibitors for treatment of TSC, retrospective and prospective studies conducted by other centres showed that TSC patients treated with mTOR inhibitors showed shrinkage of renal tumours and a greatly reduced risk of bleeding, confirming significant patient benefits from the research **[5.4]**.

As further evidence, the Tuberous Sclerosis Association estimated that up to 11,000 people in the UK live with this challenging condition, and describe the improvements to patients' quality of life: *"The impact of successful treatment of renal angiomyolipoma with mTOR inhibitors on patient quality of life has been immense as the treatment can be taken by patients orally within the comfort of their home, while previous surgical and embolization approaches required hospital admission and caused permanent damage to renal function. As it is directed to the underlying disease mechanism, the treatment also benefits patient's skin lesions and epilepsy, further contributing to improvement in quality of life"* **[5.10]**.

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

[5.1] Krueger DA and Northrup H on behalf of the International Tuberous Sclerosis Complex Consensus Group: Tuberous sclerosis complex surveillance and management:

recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Paeditric Neurology 2013 October, 49:255-265
DOI: 10.1016/j.pediatrneurol.2013.08.002

[5.2] Tuberous Sclerosis Alliance testimonial

[5.3] Letter from John Bissler MD, Health Science Centre (University of Tennessee)

[5.4] Bissler JJ, Kingswood JC, Radzikowska E, Zonnenberg BA, Frost M, Belousova E, Sauter M, Nonomura N, Brakemeier S, de Vries PJ, Whittemore VH, Chen D, Sahmoud T, Shah G, Lincy J, Lebwohl D, Budde K. Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis (EXIST-2): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet. 2013 March, 9;381(9869):817-24

[5.5] Welsh commissioning of mTOR inhibitor therapies evidence group

[5.6] Tuberous Sclerosis Association #Fight4Treatment and associated campaign materials

[5.7] NHS England Clinical Commissioning Statement

[5.8] Amin S, Kingswood JC, Bolton PF, Elmslie F, Gale DP, Harland C, Johnson SR, Parker A, Sampson JR, Smeaton M, Wright I, O'Callaghan FJ. The UK guidelines for management and surveillance of Tuberous Sclerosis Complex. QJM 2019 March, 112(3):171-182

[5.9] UK Tuberous Sclerosis website Treatment and Management page

[5.10] Tuberous Sclerosis Association UK testimonial