Institution: Cardiff University

Unit of Assessment: UoA3

Title of case study: Research drives development and use of biocompatible dialysis solutions, and better patient outcomes in peritoneal dialysis

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

More than 240,000 people with kidney failure are treated with peritoneal dialysis (PD) worldwide. Cardiff University pioneered novel test methods that identified deleterious dialysis solution components, leading directly to manufacturers introducing more biocompatible dialysis fluids that improve patient outcomes. Cardiff investigators designed and ran the early clinical studies on these new fluids, which now lead the PD solutions market worldwide, and are recommended in European clinical guidelines. Recent evidence suggests that their use reduces peritonitis severity, decreases peritonitis incidence by 40% and mortality by 30%, resulting in reduced hospitilsation and significant healthcare savings.

2. Underpinning research (indicative maximum 500 words)

1.75 million people worldwide depend on dialysis treatment: the majority of these receive haemodialysis (HD). More than 240,000 patients, however, use peritoneal dialysis (PD), which uses the patient's peritoneum (the membrane which lines the abdominal cavity) instead of an external artificial filter. PD is cheaper than HD, and has clinical and lifestyle advantages for patients. However, the complications of infection (peritonitis) and scarring of the peritoneal membrane over time (fibrosis) have prevented greater uptake of PD and limit its long-term use.

Understanding the fundamental biology underpinning PD-related peritonitis and fibrosis

Prior to this underpinning research, PD patients were treated exclusively with dialysis solutions containing a mixture of potentially injurious compounds, comprising un-physiological lactate and glucose concentrations, acidic pH and the products of glucose degradation. The effects of this milieu on the peritoneal membrane, and on the ability of the peritoneal immune response to defend against infection, were unknown, and no tools or techniques were available to measure them.

The research team in Cardiff University headed by Professors Nicholas Topley (1993-present), Gerald Coles (1993-2000), and John Williams (1993-2012) developed the necessary systems for *in vitro* and *in vivo* testing, and used these to study the effects that the different components of PD fluids have on cells in the abdomen. With funding from The Medical Research Council, The Wellcome Trust, National Institute for Social Care and Health Research (NISCHR) and Baxter Extramural Grant Program (EGP), the Cardiff team was the first to isolate and culture human peritoneal mesothelial cells and fibroblasts [3.1]. The researchers were also the first to develop animal models that mimic PD infection. Using their novel *in vitro* and *in vivo* test systems, the researchers investigated the effect of PD solution components on peritoneal leukocytes (immune cells which define infection response) and mesothelial cells and fibroblasts (cells which produce scarring and fibrosis) [3.2,3.3]. The Cardiff group performed histopathological studies using samples of peritoneal membrane from patients and established the International Peritoneal Biopsy Registry. In 2002 they produced the definitive description of how the peritoneum changes during the lifetime of patients on PD [3.4].

Development and early clinical testing of biocompatible PD fluids

Based on these studies, the Cardiff team worked with the major manufacturers to develop more biocompatible PD solutions. Researchers in Cardiff designed and led the first clinical studies of these biocompatible fluids [3.5,3.6]. Phase II/III trials of Physioneal (Baxter) and Balance (Fresenius) randomised 233 patients in a crossover manner, giving patients up to 12 months exposure to conventional or to biocompatible PD fluids. The results confirmed the clinical safety and tolerability of the new solutions. It was concluded that the use of these solutions significantly improved peritoneal membrane integrity and local peritoneal homeostasis. The data also suggested that residual kidney function was better preserved with some of the biocompatible fluids [3.6].

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

[3.1] **Topley, N.**, Jorres, A., Luttmann, W., Petersen, M.M., Lang, M.J., Thierauch, K.H., Muller, C., **Coles, G.A.**, Davies, M. and **Williams, J.D.** Human peritoneal mesothelial cells synthesize interleukin-6: induction by IL-1 beta and TNF alpha. Kidney Int. (1993) 43: 226-233.

http://dx.doi.org/10.1038/ki.1993.36

[3.2] Liberek, T., **Topley, N.**, Jorres, A., **Coles, G.A.**, Gahl, G.M. and **Williams, J.D.** Peritoneal dialysis fluid inhibition of phagocyte function: effects of osmolality and glucose concentration. J. Am. Soc. Nephrol. (1993) 3: 1508-1515. http://jasn.asnjournals.org/content/3/8/1508.long

[3.3] Witowski, J., **Topley, N.**, Jorres, A., Liberek, T., **Coles, G.A.** and **Williams, J.D.** Effect of lactate-buffered peritoneal dialysis fluids on human peritoneal mesothelial cell interleukin-6 and prostaglandin synthesis. Kidney Int. (1995) 47: 282-293. http://dx.doi.org/10.1038/ki.1995.36

[3.4] **Williams, J.D.**, Craig, K.J., **Topley, N.**, Von Ruhland, C., Fallon, M., Newman, G.R., Mackenzie, R.K., Williams, G.T. and Peritoneal Biopsy Study, Group. Morphologic changes in the peritoneal membrane of patients with renal disease. J. Am. Soc. Nephrol. (2002) 13: 470-479. Cited 442 times (222 citations since 2008). http://jasn.asnjournals.org/content/13/2/470.long

[3.5] **Coles, G.A.**, O'Donoghue, D.J., Pritchard, N., Ogg, C.S., Jani, F.M., Gokal, R., Cancarini, G. C., Maiorca, R., Tranaeus, A., De Vos, C., Hopwood, A. and Faict, D. A controlled trial of two bicarbonate-containing dialysis fluids for CAPD--final report. Nephrol. Dial. Transplant. (1998) 13: 3165-3171. http://dx.doi.org/10.1093/ndt/13.12.3165

[3.6] **Williams, J.D.**, **Topley, N.**, Craig, K.J., Mackenzie, R.K., Pischetsrieder, M., Lage, C., Passlick-Deetjen, J. and Euro Balance Trial, Group. The Euro-Balance Trial: the effect of a new biocompatible peritoneal dialysis fluid (balance) on the peritoneal membrane. Kidney Int. (2004) 66: 408-418. http://dx.doi.org/10.1111/j.1523-1755.2004.00747.x

Key funding sources

- **Topley, N.** (PI), **Williams, J.D.**, **Coles, G.A.** and **Davies, M**. The contribution of the mesothelial cell to peritoneal fibrosis. 1993-1996. Medical Research Council. £195,446.
- **Davies, M.** (PI), **Topley, N**. and **Williams, J.D**. The role of hyaluronic acid in mesothelial cell regeneration following injury *in vitro* and *in vivo*. 1999-2002. Wellcome Trust. £203,762.
- **Topley, N**. (PI), **Williams, J.D**. and **Coles, G.A**. The contribution of the mesothelium to the control of leukocyte transmigration during peritonitis. 1994-1996. NISCHR. £43,000.
- **Topley, N**. (PI), **Williams, J.D**. and **Coles, G.A**. Peritoneal Fibrosis in CAPD. 1993-1996. Baxter Healthcare Corporation, Extramural Grant Program Project Grant. $120,000.

Since 1993 the group has secured over £1 million of funding from Baxter and Fresenius to support work on PD-related topics and clinical trials. Current active grants supporting translational peritoneal dialysis research exceed £2.5M (funders include MRC, NISCHR, NIHR and EU FP7).

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

A new generation of biocompatible fluids, developed from Cardiff discoveries, is now delivering impacts worldwide including:

- Patient health - Worldwide reduction in mortality and the likelihood and severity of infection.
- New therapies - The Cardiff method is internationally accepted for evaluating new PD therapies.
- Improved practice - International guidelines recommend nephrologists use new PD solutions.
- Economic benefit - Biocompatible fluids are replacing older solutions in a $1.7billion p.a. market
- Healthcare cost benefit - Reduced hospital stays and lower peritonitis treatment costs.

Background: Advances originating in Cardiff lead to biocompatible PD fluid development

The novel discoveries and testing methods developed in Cardiff made key advances that drove and enabled new biocompatible solution development. Test systems developed in Cardiff established that the combination of low pH and high lactate concentrations inhibited host defence and cell viability and established the cellular mechanisms responsible for the negative impact of high glucose concentrations. This research led directly to the production of physiological pH PD solutions, e.g. Physioneal® (Baxter), Balance® (Fresenius), and the use of lower lactate concentrations by replacement with bicarbonate in commercial solutions, e.g. Physioneal®, Bicavera® (Fresenius). Identification of the negative consequences of high glucose concentrations and osmolality led directly to the implementation of glucose sparing therapies using glucose polymer- and amino acid-based solutions such as Extraneal® and Nutrineal® (Baxter) [5.1] in which Cardiff also played a leading role in pre-clinical development. Cardiff contributed to the establishment of glucose degradation product research that underpins new PD solution design

(Physioneal®, Balance® and Trio®). This body of work was critical to establishing a new field of PD solutions research, and led directly to the iterative development of new products in which Cardiff played a direct role [5.2-5.4], for example *"The critical contribution of Prof Nick Topley's research group at Cardiff University in the development phase of the PD solutions Physioneal 35 and 40*" (Professor Peter Rutherford, Medical Director (Renal) – Europe, Middle East and Africa Baxter Healthcare SA [5.2]). Williams, Coles and Topley acted as scientific advisors to Baxter and Fresenius (the leading PD solution manufacturers worldwide), guiding them in the composition of new solutions to reduce their detrimental effects and in the design of relevant clinical trials [3.5,3.6]. The biocompatibility and clinical trial data from Cardiff was used for the worldwide registration of Physioneal [5.2] and in all (including current) regulatory submissions for new PD solutions by Fresenius [5.3]. Professor Simon Davies, who runs the largest PD unit in the UK and is one of the foremost authorities on PD, dedicated in 2011 an international journal publication to the Cardiff's team contribution to PD research. Amongst many testaments to Cardiff's leading transformational research in this area the article states: *"The hallmark of the Cardiff contribution to our understanding of PD has been their translational approach to research, combining strong basic science with intelligent clinical questions...resulting in the development and testing of more biocompatible solutions. More than any other group, they have held the torch for basic science in PD research. These observations led to the conceptualization of biocompatibility as a local intraperitoneal process distinct from the systemic effects of PD…and became the gold standard approach to assessing the biocompatibility of newly developed PD solutions"* [5.4].

Biocompatible PD fluids improve patient outcomes and quality of life

Following early clinical trial work by Cardiff, independent studies from other centres have provided endorsement of the benefits of biocompatible fluids, and data continues to accrue in this area. In 2012 a randomised study in Australia and New Zealand compared conventional and biocompatible PD therapy in patients for two years and observed a 40% reduction in peritonitis rates. When infection did occur it was more likely to be classed as mild, and the length of stay in hospital was halved from 11 to 6 days [5.5,5.6]. In 2012, an observational study of 2163 patients in Korea noted a 30% reduction in all-cause mortality in patients using biocompatible solutions compared to a cohort using conventional fluids. The absolute risk of death per year in this study was 5.93% in the group treated with biocompatible solutions and 8.86% in those treated with standard therapy, suggesting that one life may be saved per year for each 38 patients treated with biocompatible fluid [5.7].

Biocompatible fluids are recommended in clinical guidelines

The growing recognition of the benefits of biocompatible PD solutions is highlighted by the 2011 publication of the European Paediatric Dialysis Working Group Guidelines [5.8]. The document, distributed to over 800 paediatric nephrologists worldwide, advises that biocompatible solutions with the lowest possible glucose concentration should be used in all childhood patients. The guidelines also state that solutions formulated to reduce glucose degradation and with bicarbonate as a buffer should be used to reduce systemic toxicity.

Development of biocompatible fluids has had economic impact

The peritoneal dialysis (PD) market was valued at $1.7 billion in 2008 and is expected to grow at 7% per annum to reach $2.9 billion in 2015 [5.9]. Biocompatible PD solutions are currently available worldwide for clinical use [5.2,5.3]. Marketing authorisations have been granted in territories including Europe, North America and Australasia and are currently being sought in many other countries. The Cardiff research and clinical trials provided key data for the worldwide registration and marketing authorisation for new biocompatible PD fluids [5.2,5.3] with the prescribing of biocompatible PD fluids increasing year on year. In 2010, across 17 European countries 60% of all Baxter's PD fluids prescribed were biocompatible products, translating to 38.5 million litres of Physioneal realising product sales of over £100 million. In certain European countries, including Sweden, Finland, Norway and Spain, biocompatible products have completely replaced standard glucose PD solutions and conventional fluids have been withdrawn [5.2].

Biocompatible fluids reduce healthcare costs

The use of biocompatible PD solutions generates significant healthcare cost savings. According to Kidney Health Australia, the average in-patient cost of treating PD-related peritonitis is ~AU$16-22K (~£10-15K) for an average 11.5 day admission. The Johnson studies [5.5,5.6] show that the use of biocompatible fluids halved the length of stay in hospitals to 6 days. With a rate of peritonitis

hospitalisation at 1 per 24 patient-months of therapy cost savings of $50-75 million p.a. worldwide are possible if ~60% of patients were treated with biocompatible fluids. In the UK, NICE estimates the costs associated with treating peritonitis exceed £100 million p.a. A 40% reduction in peritonitis rates from the use of biocompatible solutions [5.6] would equate to a cost saving of £24 million p.a.

A robust methodology for measuring peritoneal membrane changes
The highly cited (Section 2, [3.4]) description of the stages of peritoneal fibrosis and vascular degeneration is now accepted internationally as the scoring system to grade the effects that modifications to PD therapy have on peritoneal membrane damage. The methodology forms the basis of most comparative histopathologic studies of the peritoneal membrane in PD patients.

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

[5.1] Clinical study showing that low-glucose PD solutions improve metabolic control in diabetic patients. Li, P.K.T., Ariza, A., Culleton, B.F., Do, J-Y., Johnson, D.W., Sanabria, M., Shockley, T.R., Story, K., Vatazin, A., Yu, A.W. and Bargman, J.M. Randomized, controlled trial of glucose-sparing peritoneal dialysis solutions in diabetic patients. J. Am. Soc. Nephrol. (2013) 24: 1889-1900. http://dx.doi.org/10.1681/ASN.2012100987

[5.2] Statement from Medical Director (Renal) for Europe, Middle East and Africa, Baxter Healthcare SA. Confirming the critical contribution of Cardiff University research in the development and registration of new biocompatible PD solutions that are seeing increasing clinical use and product sales worldwide.

[5.3] Contact - Marketing Director Home Therapies, International Marketing and Medicine, Fresenius Medical Care Deutschland GmbH. Confirming the use of biocompatibility and clinical trial data from Cardiff in submissions for new product registrations of PD solutions.

[5.4] Paper from one of the most respected authorities on PD detailing Cardiff University's leading role in PD research. Davies, S.J. Peritoneal Dialysis Research In The UK: The Cardiff Contribution. Periton. Dialysis Int. (2011) 31(S2): S39–S42. http://dx.doi.org/10.3747/pdi.2010.00152

[5.5] Clinical study showing that biocompatible PD fluids delay the onset of anuria and reduce the incidence of peritonitis compared with conventional fluids in PD. Johnson, D.W., Brown, F.G., Clarke, M., Boudville, N., Elias, T.J., Foo, M.W., Jones, B., Kulkarni, H., Langham, R., Ranganathan, D., Schollum, J., Suranyi, M., Tan, S.H., Voss, D. and balANZ Trial Investigators. Effects of biocompatible versus standard fluid on peritoneal dialysis outcomes. J. Am. Soc. Nephrol. (2012) 23: 1097-1107. http://dx.doi.org/10.1681/ASN.2011121201

[5.6] Clinical study showing that biocompatible PD fluids reduce peritonitis rates in PD patients, resulting in reduced hospitilsation. Johnson, D.W., Brown, F.G., Clarke, M., Boudville, N., Elias, T. J., Foo, M.W., Jones, B., Kulkarni, H., Langham, R., Ranganathan, D., Schollum, J., Suranyi, M. G., Tan, S.H., Voss, D. and balANZ Trial Investigators. The effects of biocompatible compared with standard peritoneal dialysis solutions on peritonitis microbiology, treatment, and outcomes: the balANZ trial. Periton. Dialysis Int. (2012) 32: 497-506. http://dx.doi.org/10.3747/pdi.2012.00052

[5.7] Clinical study showing that treatment with biocompatible PD solutions is associated with improved patient survival when compared against conventional PD solutions. For example Table 5 pp 716. Han, S.H., Ahn, S. V., Yun, J.Y., Tranaeus, A. and Han, D.S. Mortality and technique failure in peritoneal dialysis patients using advanced peritoneal dialysis solutions. Am. J. Kidney Dis. (2009) 54: 711-720. http://dx.doi.org/10.1053/j.ajkd.2009.05.014

[5.8] Clinical guidelines recommending the use of biocompatible PD solutions in children. Schmitt, C.P., Bakkaloglu, S.A., Klaus, G., Schroder, C., Fischbach, M. and European Pediatric Dialysis Working, Group. Solutions for peritoneal dialysis in children: recommendations by the European Pediatric Dialysis Working Group. Pediatr. Nephrol. (2011) 26: 1137-147. http://dx.doi.org/10.1007/s00467-011-1863-4

[5.9] Increasing Incidence of End-Stage Renal Disease Driving the Peritoneal Dialysis Market, GlobalData, October 2009, pp 5-11; http://www.reportlinker.com/p0155730-summary/Increasing-Incidence-of-End-Stage-Renal-Disease-Driving-the-Peritoneal-Dialysis-Market.html

All references, testimony and webpages saved as PDFs are available from the HEI on request.