Institution: University of York		
Unit of Assessment: 5 - Biological Sciences		
Title of case study: Bladder tissue research impacts Actos multidistrict litigation bellwether case and USD2.4 billion product liability settlement		
Period when the underpinning research was undertaken: 2004 – 2020		
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:**
Jennifer Southgate	Professor	1/10/99-present
Claire Varley	Senior Research Associate Research Associate Research Fellow Research Associate	1/10/00-31/11/09 1/12/09-31/12/11 26/3/12-25/6/12 3/9/12-28/2/13
Period when the claimed impact occurred: 08/2013-2015		
Is this case study continued from a case study submitted in 2014? N		

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

The research work of Prof Jenny Southgate on the homeostasis of normal human urothelial tissue and its implications for bladder cancer led to her serving as an expert witness in a landmark class action case in US federal court about the requirement of pharmaceutical companies to disclose serious side effects from their marketed drugs. The drug in question, Actos, was prescribed over 100 million times in the US for the treatment of type 2 diabetes (at a value of USD24 billion), but exposure to the drug put patients at increased risk of developing bladder cancer. Prof Southgate's testimony for the plaintiffs, Terry and Sue Allen, contributed to a court ruling against co-defendants Takeda and Eli Lilly, with a jury awarding record punitive damages of USD9 billion, later commuted by law to USD36 billion. As one of three experts to provide causation opinions on the case, Southgate played a crucial role in refuting the claims of the defendants, based on her expert knowledge. Following this court decision in 2014, Takeda and Eli Lilly paid USD2.4 billion to settle over 9000 claims from patients, representing one of the largest product liability settlements ever in the pharmaceutical industry.

2. Underpinning research (indicative maximum 500 words)

Prof Jenny Southgate's group has had a longstanding interest in human bladder cancer, particularly how the balance (homeostasis) between cell proliferation and differentiation in the normal tissue is disrupted in cancer. To study this, Southgate and team established an in vitro experimental system using normal human urothelial cells and tissues. Investigations conducted in York from 2002 focussed on the role of a particular nuclear receptor, peroxisome proliferator-activated receptor gamma (PPARgamma), and demonstrated for the first time the critical role of PPARgamma in the specialisation (differentiation) of human urothelial cells **(3.1)**. The work was also significant in providing a direct link between the complex pathways regulating proliferation and differentiation of urothelial cells **(3.2)**. Synthetic compounds of the thiazolidinedione (TZD) class, including troglitazone and rosiglitazone, are known to be able to activate PPARgamma, and both were used experimentally in Southgate's in vitro system to induce urothelial differentiation **(3.1, 3.2)**.

Further work of the Southgate group then went on to determine the mechanism by which PPARgamma drives cells to specialise as urothelium, by activation of multiple transcription factors (FOXA1, IRF-1 and ELF3) which, in turn, switch on the overall programme for urothelial cell differentiation. In this way, the Southgate group was able to demonstrate that PPARgamma acts as a "master regulator" controlling urothelial cell specification **(3.3).** Since the publication of this work, international collaborations, including Southgate, have gone on to demonstrate the critical nature of these growth and differentiation pathways—including PPARgamma— in the development of human bladder cancer **(3.4).**

The 2004 papers on urothelial differentiation resulted in interest by multiple pharmaceutical companies developing compounds to activate PPAR for the treatment of type 2 diabetes and metabolic syndrome. Of particular concern were dual specificity PPAR activators (agonists) which are compounds that bind both PPARgamma as well as its highly related family member PPARalpha. Animal trials with these dual specificity PPARalpha+gamma agonists led to significant concerns about their use, in both Europe and the US, due to the development of bladder cancer in rodents exposed to the drugs. Studies designed to identify their Mode of Action (MoA) also raised similar concerns. The Southgate group worked collaboratively with Novo Nordisk to study the dual specificity PPAR agonist, ragaglitizar. This collaborative work developed a MoA for carcinogenesis caused by dual specificity PPAR agonists that depended on activation of the PPAR receptor, making the MoA relevant to human bladder carcinogenesis **(3.5)**. This work was important because it disputed other theories that argued rodent bladder carcinogenesis by PPAR dual agonists was of no human relevance**.**

It is due to this demonstrated expertise in the role of PPARgamma in normal urothelial tissue and human bladder cancer, as well as the study of carcinogenic effects of dual PPAR agonists, that Prof Southgate was initially contacted about serving as an expert witness in a landmark trial about Actos (pioglitazone - a PPARgamma-selective drug with alpha activity) and bladder cancer.

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

3.1. **Varley CL**, Stahlschmidt J, Smith B, Stower M, **Southgate J**. Activation of peroxisome proliferator-activated receptor-gamma reverses squamous metaplasia and induces transitional differentiation in normal human urothelial cells. Am J Pathol. 2004 May;164(5):1789-98. DOI: 10.1016/s0002-9440(10)63737-6 PubMed PMID: 15111325; PubMed Central PMCID: PMC1615665.

3.2. **Varley CL,** Stahlschmidt J, Lee WC, Holder J, Diggle C, Selby PJ, Trejdosiewicz LK, **Southgate J**. Role of PPARgamma and EGFR signalling in the urothelial terminal differentiation programme. J Cell Sci. 2004 Apr 15;117(Pt 10):2029-36. DOI: doi.org/10.1242/jcs.01042. Epub 2004 Mar 30. PubMed PMID: 15054105.

3.3. **Varley CL**, Bacon EJ, Holder JC, **Southgate J**. FOXA1 and IRF-1 intermediary transcriptional regulators of PPARgamma-induced urothelial cytodifferentiation. Cell Death Differ. 2009 Jan;16(1):103-14. DOI: 10.1038/cdd.2008.116. Epub 2008 Aug 8. PubMed PMID: 18688264.

3.4. Biton A, Bernard-Pierrot I, Lou Y, Krucker C, Chapeaublanc E, Rubio-Pérez C, López-Bigas N, Kamoun A, Neuzillet Y, Gestraud P, Grieco L, Rebouissou S, de Reyniès A, Benhamou S, Lebret T, **Southgate J**, Barillot E, Allory Y, Zinovyev A, Radvanyi F. Independent component analysis uncovers the landscape of the bladder tumor transcriptome and reveals insights into luminal and basal subtypes. Cell Rep. 2014 Nov 20;9(4):1235-45. DOI: 10.1016/j.celrep.2014.10.035. Epub 2014 Nov 13. PubMed PMID: 25456126.

3.5. Egerod FL, Svendsen JE, Hinley J, **Southgate J**, Bartels A, Brünner N, Oleksiewicz MB. PPAR alpha and PPAR gamma coactivation rapidly induces Egr-1 in the nuclei of the dorsal and ventral urinary bladder and kidney pelvis urothelium of rats. Toxicol Pathol. 2009 Dec;37(7):947-58. DOI: 10.1177/0192623309351723. PubMed PMID: 20008548.

Indicators of quality

- All outputs **3.1-3.5** published in peer-reviewed journals
- **3.1** and **3.2** funded by Wellcome Trust (peer-reviewed grants)
- **3.1** and **3.2** returned in RAE 2008; 3.3 returned in REF 2014

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

To combat the increasing rates of type 2 diabetes in industrialised countries, drugs of the thiazolidinedione (TZD) class, including troglitazone and rosiglitazone, have been widely used to help patients improve control of blood sugar levels. This class of drugs is known to activate a specific receptor, peroxisome proliferator-activated receptor (PPAR), and more specifically of subtype PPARgamma, and thus are known as PPARgamma agonists. Further drugs were later developed to target multiple PPAR subtypes, including both PPARgamma and PPARalpha, so-called dual-specificity agonists. The drug pioglitazone (marketed as "Actos") was one such drug developed by Takeda Pharmaceuticals and Eli Lilly which went on the market in 1999. Sales of Actos in the US have exceeded USD24 billion since 1999, corresponding to more than 100,000,000 prescriptions.

As described above, preclinical work showed that rodents exposed to Actos were at increased risk of developing bladder cancer. Although Actos was initially available in other jurisdictions, in 2011 it was withdrawn from France and Germany due to concerns over risks to patients taking Actos of developing bladder cancer. This case study focuses on the impact Southgate's research had in the US because this is where Actos continued to be prescribed and thus where the ensuing litigation occurred.

In 2011, the US Federal Drug Administration (FDA) updated its drug labelling for Actos for both healthcare professionals and patients, to reflect the possible risk of bladder cancer. In 2016 the FDA issued a safety announcement concluding that pioglitazone may be associated with an increased risk of urinary bladder cancer based on a number of clinical studies.

During this same time, litigation was underway in the United States involving thousands of individuals who claimed to have developed bladder cancer from using Actos; at one point there were more than 5,000 cases in federal court and another 4,500 cases in state courts. These federal cases formed the basis for a multidistrict class action litigation, with plaintiffs Terry and Sue Allen selected to represent the first bellwether case against co-defendants Takeda and Eli Lilly (ALLEN v. TAKEDA Case No 12-cv-0064). The case was held in the Western District of Louisiana federal court in Lafayette in April 2014 where Southgate served as an expert witness and gave testimony critical to the outcome of the litigation in favour of the plaintiffs. This went on to become a landmark trial case as the jury made the largest ever award of punitive damages against a pharmaceutical company (USD9 billion, **5.1**) and later, this became one of the largest product-liability settlements in the pharmaceutical industry (USD2.4 billion, **5.2**).

The presiding judge in the case, Judge Rebecca Doherty, appointed attorney Paul J Pennock, a member of the Plaintiff's Steering Committee, as co-lead counsel of the Plaintiffs' Executive Committee. Attorney Stephanie O'Connor was also appointed to the Plaintiffs' Steering and Executive Committees and was named as the "Science Coordinator". In 2013, Ms O'Connor contacted Southgate as a potential expert witness on the relevant science and medicine supporting the causal connection between Actos and bladder cancer. O'Connor had identified Southgate as an expert to give her opinion on how exactly the effects of Actos could exert "off target" effects that could lead to the development of urothelial cancer **(5.3)**. The identification of Southgate as a potential expert witness was due to her publications showing the role of PPARgamma in urothelial differentiation **(3.1, 3.2)**. Southgate was one of three experts to provide causation opinions at the trial (also including pharmaco-epidemiology and uro-oncology), with Southgate addressing mechanistic molecular biological issues **(5.4)**.

Southgate wrote an expert report dated 6 August 2013 **(5.5)** describing the different studies and data that supported a role for Actos in bladder tumorigenesis; this expert report was proffered to the Court in August 2013 and marks the initial timing of the impact that Southgate had on the litigation. Following an expert witness deposition under a Daubert motion in January 2014, Judge Doherty upheld Southgate as an expert who was qualified to give an opinion on the case **(5.6)**. Thereafter Southgate provided sworn testimony in court during the trial in February 2014. There were four important aspects of Southgate's testimony that addressed causation based on the relevant molecular biology. Firstly, Southgate was able to refute the assertion of the

defendants that Actos was only specific for PPARgamma by describing the relevant evidence on the dual specificity of Actos for PPARgamma and PPARalpha. Secondly, Southgate also gave testimony based on her own research that the dual specificity agonists demonstrated carcinogenic effects on bladder epithelium **(3.5).** Thirdly, she was able to dispute the defendants' argument that bladder carcinogenesis in rodents was not relevant to humans by demonstrating from her own research the importance of PPARgamma in human urothelium **(3.1-3.3)**. Finally, Southgate also addressed issues of latency of tumour formation and mechanism, rebutting the defendants' assertions that the timing of bladder cancer in rodents exposed to Actos did not have relevance in humans. O'Connor's described Southgate's contribution as follows: "Dr Southgate was successfully able to bridge the gap between experimental data and human physiology, providing further support for the findings of elevated bladder cancer risk as reported in several observational studies." **(5.3)** The relevance of this is confirmed by Pennock comments: "Dr. Southgate's research confirming the receptor-mediated effects of PPARs in experimental systems and therefore the potential for this class of drugs to cause bladder cancer in humans was a crucial piece of evidence in order for the case to succeed." **(5.4)**

The jury decided in favour of the plaintiffs Terry and Sue Allen, awarding USD1.47 million in compensatory damages. They further imposed punitive damages against co-defendants Takeda and Eli Lilly of USD6 billion and USD3 billion, respectively. As the largest punitive damages (USD9 billion) ever awarded in history by a jury against the pharmaceutical industry, the result of the trial sent a warning shot to the industry where, as stated by the judge it reflected "a high degree of reprehensibility of the Defendants' conduct and the need to adequately deter such conduct in the future". **(5.1)**

These punitive damages were later commuted by the judge to USD27 million and USD9 million, respectively under the Fifth Circuit's "maximum recovery rule", but the judge awarded what she determined is the "maximum amount allowed by the substantive wrong of the Due Process Clause under the facts of this case." **(5.1)** The defendants were denied a retrial.

O'Connor described the material contribution Southgate made to the success of the trial: "The combination of Dr Southgate's vast knowledge of the relevant subject matter (urothelium and urothelial tumorigenesis), her clear and concise presentation of the evidence on direct examination, her ability to admirably withstand vigorous cross-examination by defence counsel all contributed to the great success of the case." **(5.3)** Pennock adds: "...the jury returned a record-breaking verdict after a two-month trial that we believe was supported by compelling evidence elicited from Dr. Southgate's research on this topic." **(5.4)**

Following the ruling in the multidistrict litigation, in 2015 Takeda paid USD2.4 billion (GBP1.6 billion) into a global fund to settle the more than 10,000 claims against Takeda involving Actos; this settlement is one of the largest product liability settlements in the pharmaceutical industry **(5.2, 5.7)**. The settlement of 9820 claims for USD2.4 billion in 2015, is an average of USD245,000 per claimant (but differing amounts would be awarded to individual claimants based on the extent of injury, dosage and length of time taking Actos; **5.2**). Takeda did not admit liability.

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

5.1. Final ruling by Judge Doherty

5.2. Master Settlement Agreement between Takeda and plaintiffs' counsel, dated 28 April 2015.

5.3. Letter from Stephanie O'Connor, partner for law firm Douglas and London, nurse-attorney and "Science Coordinator" on the Plaintiffs' Steering and Executive Committees for the Multidistrict Litigation in federal court "Actos (Pioglitazone) products liability litigation (MDL-2299)."

5.4. Letter from Paul J Pennock, then a partner at law firm Weitz and Luxenberg, and appointed by US District Judge Rebecca Doherty as co-Lead counsel on the Plaintiffs' Executive Committee for "Actos (Pioglitazone) products liability litigation (MDL-2299)"

5.5. "Actos (Pioglitazone) Products Liability Litigation (MDL 2299)—Expert Report" authored by Southgate and submitted to Stephanie O'Connor on 6 August 2013.

5.6. "Memorandum Ruling: Jennifer Southgate, Ph.D." by Judge Doherty, 6 January 2014.

5.7. "Takeda Agrees to Pay $2.4 Billion to Settle Suits Over Cancer Risk of Actos", New York Times, 28 April 2015, https://www.nytimes.com/2015/04/29/business/takeda-agrees-to-pay-2-4-billion-to-settle-suits-over-cancer-risk-of-actos.html