Institution: University of Kent and University of Greenwich

Unit of Assessment: 3 Allied Health Professions, Dentistry, Nursing and Pharmacy.

Title of case study:
Novel models for advanced imaging of urinary system function in healthy and diseased tissue.

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

Drs Peppiatt-Wildman & Wildman have developed novel models to investigate kidney and bladder function and drug action, through visualisation of cellular events in live tissue. This has had an immediate impact on research in the Pharmaceutical Industry, resulting in collaborative links with Pfizer USA and Biogen Idec, and significant investment by Pfizer on the application of kidney models in the development of novel lead candidate drugs for the treatment of kidney disease. In addition, imaging of live bladder tissue, adapted for bedside application, has altered clinical practice in continence and nephrology clinics in NHS Trusts.

2. Underpinning research (indicative maximum 500 words)

Current methods for assessing kidney and bladder function in health and disease are limited by a lack of appropriate technology and methodology, relying on crude *in vitro* systems and post-hoc measurements such as cell necrosis in patient biopsies. These limitations have significantly hampered the ability of physiologists and clinicians to better understand basic urinary system physiological function, processes occurring in the onset and progression of disease or in response to drug-toxicity, all of which pose a real and significant clinical problem.

The onset of this work was facilitated by a Career Development Award to Peppiatt-Wildman by the MRC, one of the 9% of projects funded that year (£1.2 million, 2007, transferred to Kent in 2012), and a number of 'linked' project grants by the Wellcome Trust in 2008, one of which was awarded to Wildman. Since 2008, initially at the Royal Veterinary College in London and latterly, here at Medway School of Pharmacy (MSOP), Peppiatt-Wildman and Wildman's research groups (collectively the Urinary System Physiology Unit) have focused on identifying and validating novel experimental models and methodologies. Wildman's group moved to MSOP in 2011 and Peppiatt-Wildman's in 2012 and, since moving, have been supported by further funding awards from the Wellcome Trust, BBSRC, MRC and Kidney Research UK for their research. The work at MSOP has led to advanced imaging of live *ex vivo* kidney slices, isolated perfused kidneys, human bladder biopsies, and urinalysis and implementing these to: *i)* advance the understanding of basic physiological processes in the kidney and bladder *ii*) delineate the mechanisms underlying kidney dysfunction, whether in the context of renal disease or drug-induced nephrotoxicity *iii)* provide industrial partners with an established experimental (screening) model that represents a new tool/approach for identification of novel drug-target sites for new or existing therapies *iv*) provide clinicians with 'better' urinalysis, primarily bedside tests, to facilitate diagnosis and more informed treatment strategies.

Application of the live *ex vivo* (and *in vivo*) kidney, live *in vitro* bladder models and urinalysis, in combination with advanced imaging approaches (e.g. multiphoton imaging of multiple readouts of cell function) have enabled the group to demonstrate preserved vascular, tubular, smooth muscle and urothelial, function in kidney and bladder models, which is representative of the *in vivo* setting, thus validating the models (3.1). The primary, defining, paper describing the methodology for live kidney slices (3.1) originated from Peppiatt-Wildman at MSOP and was recognised by the Faculty of 1000 as being of special significance in its field.

In subsequent research, these models have been used to: *i)* define novel regulatory mechanisms of blood flow control in the kidney *i.e.* pericyte-mediated regulation of renal medullary blood flow at the capillary level *ii)* demonstrate tubulovascular and neurovascular cross-talk in the kidney (3.2, 3.3, 3.4), *iii)* demonstrate an infectious component to a significant subset of overactive bladder (OAB) patients (which is now informing the clinical definition of OAB), and *iv)* gain a better

understanding of recurrent urinary tract infections (UTIs) in renal transplant patients, whilst proposing a superior diagnostic test for UTIs in this sensitised and vulnerable cohort (3.5).

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

3.1) **Crawford C,** Kennedy-Lydon T, Sprott C, Desai T, Sawbridge L, Munday J, Unwin RJ, **Wildman SS, Peppiatt-Wildman CM**. An intact kidney slice model to investigate vasa recta properties and function in situ. *Nephron Physiol.* 2012, 120(3):17-31. ***Faculty 1000 recommended.***

3.2) **Peppiatt-Wildman CM**. The evolving role of renal pericytes. *Curr Opin Nephrol Hypertens*. 2013, 22:10-16.

3.3) Kennedy-Lydon TM, **Crawford C, Wildman SS, Peppiatt-Wildman CM**. Renal pericytes: regulators of medullary blood flow. *Acta Physiol (Oxf).* 2013, 207:212-225.

3.4) **Peppiatt-Wildman CM**, **Crawford C**, Hall AM. Fluorescence Imaging of Intracellular Calcium Signals in Intact Kidney Tissue. Nephron *Exp Nephrol.* 2012, 121(1):49-58.

3.5) Harber M, Malone-Lee J, **Wildman S**. Asymptomatic bacteriuria and urinary tract infection in renal transplantation. Brit J Renal Medicine. 2012, 17(1):4-7.

Highlighted authors based at Medway School of Pharmacy.
Underlined authors healthcare professionals at NHS Trusts.

Related Grants held at MSOP:

Peppiatt-Wildman CM. Pericyte-mediated intra-renal blood flow regulation: from brain to kidney MRC £105,624 (2012).

Wildman S. Luminal fluid regulation of renal tubular transport mechanism: P2 receptor control of sodium and water. Wellcome Trust £80,481 (2012).

Peppiatt-Wildman CM. Unravelling the mechanisms of non-steroidal anti-inflammatory induced nephrotoxity. Kidney Research UK £198,252 (2013).

Wildman S. A proof of concept, longitudinal, comparative, observational study of urinary epithelial cell infection in renal transplant patients and asymptomatic controls. Kidney Research UK £28,897 (2013).

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

Impact on Commerce

Peppiatt-Wildman and Wildman's unique approaches to investigate kidney and bladder function in a range of experimental models, including tissue slices, isolated and perfused organs, and urine have received substantial industrial financial support and so this research has had demonstrable impact on commerce.

Initial research using the novel kidney-slice methodology was presented in an 'invited speaker' acute kidney injury session at the American Society of Nephrology 'Renal Week' meeting in 2011, a meeting which attracts ~13,000 international clinicians and researchers. This presentation resulted, subsequently, in collaborative links being initiated with Pfizer USA and a collaborative research contract based on the application of the model to better understand acute kidney injury (AKI) is now in place at MSOP (Pfizer contract worth £528K, 5.1). Research at Pfizer has been directly influenced, therefore, by the possibilities opened up through use of this novel model and

Pfizer have invested in this now because of its immediate potential for discovering new lead compounds for kidney disease (5.2).

In 2012, collaborative links were initiated with Biogen Idec (USA) and a pilot project, supported and funded by Biogen Idec (5.3), to investigate novel therapies in AKI is now underway to provide preliminary data for an MRC MICA application. The direction of Biogen Idec's research programme has, therefore, been directly influenced by the research collaboration with Peppiatt-Wildman and Wildman (5.4).

Thus the focus and direction of research in two separate pharmaceutical companies has been directly influenced by the research of Peppiatt-Wildman and Wildman and these companies have *invested in research and development* as a direct result of this work. This emphasises the requirement for Pharmaceutical companies to engage with Peppiatt-Wildman and Wildman in order to develop this model for their own internal use. In the longer term, it is envisaged by both MSOP and industry that the impact of these two industry collaborations will be identification of novel therapeutics for AKI.

Impact on Clinical Practice

The novel approaches developed have also made an impact on clinical practice. Peppiatt-Wildman and Wildman initiated collaborative links with the Centre for Nephrology at UCL in order to identify how this novel model and methodology might be applied to address specific clinical problems. Their methodology was used to address a highlighted clinical problem of drug-induced nephrotoxicity that was observed in a wide cross section of patients exposed to non-steroidal anti-inflammatory drugs and also in HIV patients being treated with anti-retrovirals. This pioneering research not only addresses a costly clinical problem but also demonstrates how this model can be used to characterise other known cases of drug-induced nephrotoxicity. Both Peppiatt-Wildman and Wildman hold Honorary positions in the Division of Medicine at UCL and provide lectures to renal clinicians, including the Renal Physiology for Clinicians accredited CPD course, which informs clinicians of new and apposite basic and clinical renal research.

In 2012 Peppiatt-Wildman and Wildman began working with nephrologists at Kent and Canterbury Hospital to address nephrotoxic side-effects associated with immunosuppressant medication commonly prescribed to renal transplant patients. This work has resulted in an internal review of combination drug therapies and funding from Kidney Research UK. Additionally, research into the chronic recalcitrant UTIs associated with renal transplant patients (using advanced urinalysis imaging), has instigated a local trial of a series of 'bedside' tests, using standard microscopy, to help identify patients likely to present with recurrent UTIs. This work has also resulted in funding from Kidney Research UK to implement a longitudinal, comparative, observational study. Nephrologists at Kent and Canterbury Hospital began *developing new diagnostics for recurrent UTIs in renal transplant patients,* involving simple imaging, and *have altered clinical practice* as a result of this research collaboration (5.5).

Also in 2012, Peppiatt-Wildman and Wildman began investigating the aetiology of OAB using advanced imaging methodologies, in collaboration with clinicians at Medway NHS Trust. The research collaboration focuses on the aetiology of OAB, a comprehensive search for biomarkers, and developing better 'bedside' tests, of which the most promising involve simple imaging. As a direct result of the collaboration, a laboratory has now been established at Medway NHS Trust Outpatients Department. This serves primarily as an adjunct to continence clinics providing rapid, cost-effective, 'bedside' urinalysis (including imaging of fresh urine samples) to inform treatment strategies. *In a short period of time this research collaboration has altered clinical practice* (5.6).

Thus the impact of this research in clinical practice is the identification of a broader range of superior diagnostics that provides clinicians with the enhanced capacity to improve the health outcomes of their patients.

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

5.1) Pfizer US Contract awarded to CM Peppiatt-Wildman, £528k, October 2012-October 2015. Title 'Components of the innate immune system are mediators of tissue ischemia by altering mitochondrial function and regulating microvessel tone in acute kidney injury'

5.2) Announcement of support from Pfizer USA (Dr N Pullen)
(http://www.msp.ac.uk/about/news/current/research-biosciences/urinary-physiogroup/pfizer-research-collaboration.html)
"Medway School of Pharmacy is to undertake a half million pound research project with the pharmaceutical company Pfizer (USA) to develop new therapies for patients that have developed Acute Kidney Injury (AKI) regardless of the initial insult. Dr Claire Peppiatt-Wildman will collaborate with Dr Nick Pullen at Pfizer's US research base on the three-year research project. It is hoped that this research project will lead to a better understanding of the precise pathophysiological mechanisms underlying AKI and identify potential novel target sites to aid the future development of preventative strategies and effective therapies."

5.3) Biogen Idec contract awarded to CM Peppiatt-Wildman. Agreed, Spring 2013.

5.4) Statement of support from Biogen Idec (Dr L Burkly)
'The direction of Biogen Idec's research programme has been influenced by the research collaboration with The Urinary System Physiology Unit'

5.5) Letter of support from Kent and Canterbury Hospital (Dr Chris Farmer)
"Our collaborative work with Wildman and Peppiatt-Wildman ensures the provision of Impact in the form of altered clinical practice."

5.6) Letter of support from Medway NHS Trust (Professor Jonathan Duckett)
Change in clinical practice as a result of research. "Used to inform treatment strategies, the novel urinalysis is a direct result of our collaborative research activities. In a short period of time this research collaboration has altered our clinical practice."