Fellows Day 2019 Meeting Report
Acknowledgements

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Kidney Research UK Fellows Day provides a unique opportunity for students, patients, clinicians, scientists and industry partners to interact, and is frequently described as the best meeting in the UK renal calendar. Kidney Research UK relies on key partnerships to drive research forward, with funding bodies including the Medical Research Council (MRC), the Stoneygate Trust, the Chief Scientist Office and the Daphne Jackson Trust. This collaboration with industry partners has enabled the development of the National Unified Renal Translational Research Enterprise (NURTuRE) – the first UK kidney biorepository, which holds samples and clinical data from over 3,000 patients with chronic kidney disease (CKD). This exciting new resource will soon be available to all researchers.

At this year’s meeting we enjoyed a diverse range of topics and speakers, including patient, academic, and industry keynote presentations. In the academic keynote presentations, Professor Jürgen Floege (Aachen University, Aachen, Germany) shared fascinating insights into glomerular disease, highlighting the need for supportive care to help patients in all aspects of life. Professor Adeera Levin (University of British Columbia, Vancouver, Canada) described important ongoing work to unpick geographical differences in health outcomes, particularly in cases of CKD of unknown origin. Professor John McMurray (University of Glasgow, Glasgow, UK) gave a comprehensive overview of new therapies available for patients with CKD and cardiovascular disease.

£8.5m
Invested in research
2018/19

Meeting report
The 19th annual Kidney Research UK Fellows Day took place at the University of Leicester (12–13 September 2019) and was chaired by Professor John Feehally.
Cardiovascular disease and diabetes

Several presenters described the application of new technological approaches in their research. Dr Jennifer Lees described a novel magnetic resonance imaging sequence, proton density-weighted, in-phase stack of stars (MRI-PDIP-SOS), to detect thoracic aortic calcification, a surrogate marker for cardiovascular disease in patients with renal disease. In a study of 90 patients, MRI-PDIP-SOS was comparable to computed tomography (the current gold-standard), allowing the evaluation of thoracic aortic calcification without the need for exposure to potentially hazardous ionising radiation.

To better understand how the kidneys control blood pressure, Ioannis Stasinopoulos is developing a mass spectrometry imaging method to map corticosteroid distribution in the kidneys. The method has so far successfully detected steroids in renal tissue, and will now be validated and applied to compare physiological adaptations to high- and low-salt diets.

Dr Robert Pope is combining mathematics and biology to help identify new drugs for the treatment of diabetic kidney disease. By using information theory to assess the reliability of insulin sensing, compounds with potentially clinically beneficial effects on podocyte insulin signalling should be more easily identified.

Chronic kidney disease

Women with CKD stages 3–5 have significantly higher rates of all adverse pregnancy outcomes than those without CKD. Given that current risk estimates are outdated and don’t allow for personalised predictions, Elizabeth Ralston and the PREDICT team are developing a tool to predict how much kidney function women are likely to lose in pregnancy. Results from the preliminary dataset have shown that pre-pregnancy estimated glomerular filtration rate and protein:creatinine ratio are significant predictors of postpartum decline in renal function. They plan to strengthen the model with an enriched dataset, before performing external validation.

CKD is often associated with loss of muscle, leading to functional impairment and a reduction in patients’ quality of life. Researching the effect of dietary protein intake on skeletal muscle mass in non-dialysis CKD, Eleanor Gore’s initial findings indicate that increased protein intake has a favourable effect on muscle preservation and functional impairment without detriment to kidney function. Dietary advice can be confusing for people with kidney conditions, so further research on this topic will be valuable for patients. Katherine Robinson is researching the role of microRNAs (miRs) in CKD-associated muscle wasting. Comparing differences in miR expression between patients with CKD and healthy controls has led to the identification of a miR, which could provide a therapeutic target for this patient population.

Kidney failure, kidney injury and fibrosis

Renal fibrosis (scarring of the kidney) is the primary cause of kidney disease. To investigate the relationship between inflammation, fibrosis and metabolism, Azadeh Harzandi is using a mouse model of CKD following acute kidney injury. RNA sequencing and transcriptomic analyses comparing mice with CKD with age-matched controls has indicated that the inflammatory response is negatively correlated with fatty acid metabolism and oxidative phosphorylation.

Researching the effect of senescent cells on post-injury fibrosis, Dr Eoin O’Sullivan has shown that senescent renal epithelial cells in vivo display marked transcriptional heterogeneity, clustering into early, intermediate, and late senescent phenotypes. It is hoped that these findings will allow drivers of senescent subtype transition to be identified and targeted therapeutically.

Dr Kevin Loudon presented his research on fibrosis caused by urinary tract infections, particularly the role of the epidermal growth factor receptor ligand amphiregulin (AREG). AREG was shown to contribute to defence against kidney infection and was upregulated in urinary tract infection-induced kidney fibrosis.

Transplantation and regenerative medicine

Post-transplantation organ rejection remains a substantial risk. Dr Joanna Hester is investigating the molecular mechanisms that regulate the immune response in the context of transplantation, with the hope of one day removing the need for powerful immunosuppressive drugs.

Addressing ischaemia reperfusion injury resulting from transplantation, Ms Victoria Banwell presented data illustrating the role of miR-214. Following injury, the level of miR-214 was significantly increased highlighting a potential role in early injury and inflammatory response. Further investigation of this potential therapeutic target is planned.
Kidney organoids are a potential alternative to transplantation with a donor kidney. Sophie Ashley and Dr Anwar Palakkam each presented research on the development of kidney organoids. Sophie successfully co-cultured ureters with kidney precursor cells, demonstrating a positive effect of the ureter on differentiation of the adjacent kidney. Aiming to generate anatomically realistic kidney organoids from stem cells, Anwar presented promising data showing the generation of organoids with a single branched collecting duct with connected nephrons and blood vessel formation.

**Inherited diseases**

Nephronophthisis (NPHP) is a genetic disorder affecting the cilia in the kidneys, which ultimately leads to end-stage renal failure. Currently, dialysis and transplantation are the only treatment options. Dr Simon Ramsbottom and Dr Elisa Molinari each presented data on the use of exon-skipping as a potential therapy for NPHP. Joubert syndrome is a ciliopathy that often involves NPHP alongside other features and is caused by mutations in CEP290. In a mouse model of Joubert Syndrome, as well as in patient cells, use of an antisense oligonucleotide to skip a mutation-containing exon in CEP290 enabled restoration of functional protein, and rescue of cilia morphology and composition. This extremely promising first example of exon-skipping technology in the kidneys indicates that it is possible to treat NPHP with antisense oligonucleotides.1

The focus of Dr Neil Roberts’ fellowship has been to further understand the pathophysiology of urofacial syndrome, a congenital bladder disease that can result in end-stage renal failure if untreated. By generating two mouse models of the disorder, Neil has demonstrated neurogenic defects in affected bladders. Neil presented functional evidence that urofacial syndrome is a peripheral neuropathy, with the bladder body failing to contract properly and outflow failing to relax properly in affected mice. These findings are paving the way towards designing novel treatments for this congenital disease, in pre-clinical models.

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**Patient keynote speaker**

**Profile: Maddy Warren**

In this year’s patient keynote speech, Maddy gave a fresh perspective on dialysis and described how she went “from surviving to thriving”. Emphasising the importance of fitness, wellbeing and exercise in living with kidney disease, Maddy skydives competitively with Fireflies Skydiving Team and completed the 2018 London Marathon.

After being diagnosed with focal segmental glomerulosclerosis (FSGS) when she was 13 years old, Maddy has now been undergoing dialysis for 21 years. Initially, peritoneal dialysis helped her to reclaim her independence, allowing her to complete her time at school. Subsequently, it was hoped that receiving a kidney transplant from her father would be the solution, allowing her to go to university and lead a healthy ‘normal’ life. Unfortunately, in what Maddy describes as the worst 6–8 months of her experience with kidney disease, her FSGS came back very aggressively and the transplant never worked.

Using her own example, she highlighted the need to keep an open mind and manage expectations, especially regarding transplantation, which is a treatment not a cure, and certainly not the ‘magic fix’ she’d been hoping for. This period of her life cemented the importance of resilience and mental strength, and she encouraged healthcare professionals to help patients focus on other things in their life, not just their disease. At this difficult time, she also accepted that for her, dialysis would be for life and she began to research and discuss with her healthcare team “what is the best quality long-term dialysis?”. Now Maddy manages her own nocturnal home haemodialysis, typically undergoing 6–7 hours while she sleeps, at least five times per week. Although this might seem daunting, Maddy stressed the need to focus on the potential lifestyle gains rather than the burden being undertaken. Because she receives at least 35 hours of high-quality haemodialysis per week, she can eat and drink what she likes. She also has the freedom to be flexible, not being tied to a timetable of attending clinic. Many of the side effects and long-term complications of dialysis are also minimised. Praising her care team, Maddy described how she had been encouraged to take ownership of her own care from day one. Seeing this as key, she urged healthcare professionals to “trust patients to make decisions about their own treatment”.

**What is focal segmental glomerulosclerosis?**

Focal segmental glomerulosclerosis (FSGS) is a family of diseases that involve damage to the glomeruli in the kidneys. Scarring to the glomeruli caused by this damage impacts on their functioning, allowing protein to leak into the urine. FSGS is a cause of nephrotic syndrome, a collection of symptoms resulting from kidney damage, and can affect children and adults.

Although in some cases FSGS is caused by an inherited disease or by an immune disorder, often the cause is unknown.
Ellen Castle

Winner of the 2019 Trevor Cook Award
King’s College London (Kidney Research UK Clinical Allied Health Professional Fellow)

Celebrating the life and contribution of Trevor Cook, a former chair of Kidney Research UK’s Lay Advisory Committee, this award recognises excellently communicated research from the lay audience’s perspective. When presenting the award, Patricia Gooden (Lay Advisory Committee) praised Ellen’s ability to clearly demonstrate the relevance of her research to patients.

Weight gain during the first year after kidney transplant increases the risk of negative outcomes such as cardiovascular disease. Tackling this problem, Ellen is creating an online resource to help transplant recipients manage their physical activity and maintain a healthy weight. After testing and feedback from transplant recipients and renal healthcare specialists, version 2 of the resource is now being developed and will be assessed in a randomised controlled trial. The Weight Gain Prevention Exercise in Renal Transplant Online study (ExeRTiOn2) will enrol transplant recipients within 3 months of receiving a transplant and follow them over one year, comparing feasibility and health outcomes with patients receiving the usual standard of care. At this stage, the resource targets specifically the first year after transplantation to prevent potentially harmful weight gain. In the future, however, it could be available to help people further along in their transplantation journey to live a healthy lifestyle.

Dr Sarah Howles

Best oral presentation
University of Oxford (Kidney Research UK Research Project Award recipient)

By undertaking the largest genome-wide association study of kidney stone disease to date, Sarah has identified common genetic risk factors that can hopefully facilitate the development of targeted therapies.

By the age of 70 years, 20% of men and 10% of women will form a kidney stone. Of those affected, up to half will go on to form a second stone, and for some the stones are highly recurrent. Although the cause can be identified in a minority of cases, most affected individuals are idiopathic stone-formers for whom treatment is generic and relatively ineffective. Furthermore, recurrent treatment for kidney stones leads to renal function decline.

Sarah and her colleagues have identified two key pathways involved in the pathogenesis of kidney stones – vitamin D metabolism and calcium-sensing receptor signalling (CaSR). First, a significant locus at CYP24A1 (a gene involved in vitamin D metabolism and calcium homeostasis) was identified. When assessed in a cohort of patients, this variant was found to correlate with serum calcium concentration and the number of kidney stone episodes. Second, five significant loci were identified in the CaSR pathway, one of which was found to correlate with urinary calcium excretion in a cohort of patients.

Both pathways provide targets for precision medicine approaches in patients with recurrent kidney stones. For example, stone-forming patients carrying the CYP24A1 variant can be advised to restrict vitamin D intake.

Adam Hurt

Best rapid poster presentation
University of Leicester Kidney Research UK Intercalated Degree Award recipient

Tasked with communicating research, relevance and key results in just 3 minutes, Adam brilliantly met the brief of the rapid poster presentations. Addressing the complex problems associated with the sedentary lifestyle of patients receiving haemodialysis, Adam presented compelling data showing potentially significant cost savings for the NHS.

Patients who undertook exercise during haemodialysis (intradialytic cycling) had significantly lower mean healthcare costs than patients receiving standard dialysis care, having fewer hospital admissions and shorter durations of stay. The important question of emotional health and wellbeing was brought up in the Q&A session, with data from this retrospective study also indicating an improvement in quality of life in patients who participated in intradialytic cycling (measured by quality-adjusted life-years [QALYs]).
News from Kidney Research UK

Sandra Currie, Kidney Research UK Chief Executive and Dr Maria Tennant, Kidney Research UK Head of Communications

Heralding a new era for Kidney Research UK, Sandra described the organisation’s strategy for 2020–2030. Not content with steady growth, Sandra wants to see significant growth from the £8.5 million invested in research in 2018/2019. The new strategy focuses on three key pillars and aims to translate research innovations into healthcare faster.

- Prevent kidney disease
- Stop, slow, reverse and repair kidney damage
- Transform treatments that replace, restore or regenerate kidney function

Maria emphasised the importance of working together to support the strategy – people want to hear about the important research being undertaken, and Kidney Research UK can help to amplify this. Research stories can be shared through external media, on the newly re-designed website, on social media channels and through the charity’s magazine Update, which goes out to 44,000 supporters, three times a year.

Keynote industry speaker

Professor Tim Johnson, Director Fibrotic Remodelling, UCB Biopharma

Tim began investigating the role of transglutaminase 2 (TG2) in kidney fibrosis while undertaking his first post-doctoral position at the Sheffield Kidney Institute, University of Sheffield. In what he describes as a major springboard for his career, Tim was awarded a Kidney Research UK Senior Fellowship in 2000, establishing his research career and enabling him to develop a research programme in kidney fibrosis and especially TG2. He has been Professor of Kidney Science at the University of Sheffield since 2012, a position he now holds with honorary status after he joined UCB Biopharma in 2013 to help develop the company’s fibrosis platform. He now holds the position of Director, Fibrotic-Remodelling.

TG2 is a wound response enzyme, which plays a key role in extracellular matrix homeostasis. Upregulation, extracellular trafficking and increased activity of TG2 correlates with the progression of fibrosis in CKD. As such, TG2 is a potential therapeutic target for the prevention of tissue scarring and thereby disease progression.

Collaboration with industry partners at various stages has been crucial in Tim’s journey to bring a TG2 inhibitor from bench to bedside. An award from LifeArc (formally MRC Technology) allowed him and his team to screen more than 10,000 hybridomas, resulting in the identification of thirteen inhibitory antibodies that specifically target TG2, three of which were fully humanised by LifeArc. UCB Biopharma licensed the TG2 antibody programme, which then allowed him to access resources needed to take the next steps to bring these therapeutics to the clinic. For example, accessing sufficient quantities of antibody was a potential obstacle for key experiments, but a collaboration between the University of Sheffield, LifeArc and UCB Biopharma enabled the project to progress. By utilising UCB’s antibody production technologies in conjunction with the University of Sheffield’s in vivo modelling capabilities, it allowed the generation of key pre-clinical data essential for regulatory documentation.

A phase 2 trial of the lead TG2 inhibitory antibody (Zampilimab, UCB7858) in adult kidney transplant recipients with post-transplant graft fibrosis (clinicaltrialsregister.eu number: 2017-004807-31) is currently underway, and Tim hopes to return to Fellows Day within the next few years to present the results.

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Save the date

Join us for Fellows Day 2020
Monday 7 and Tuesday 8 September 2020
University of Edinburgh