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Integrating basic science with translational research: the 13th International Podocyte Conference 2021

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The 13th International Podocyte Conference was held in Manchester, UK, and online from July 28 to 30, 2021. Originally planned for 2020, this biannual meeting was postponed by a year because of the coronavirus disease 2019 (COVID-19) pandemic and proceeded as an innovative hybrid meeting. In addition to in-person attendance, online registration was offered, and this attracted 490 conference registrations in total. As a Podocyte Conference first, a day for early-career researchers was introduced. This premeeting included talks from graduate students and postdoctoral researchers. It gave early career researchers the opportunity to ask a panel, comprising academic leaders and journal editors, about career pathways and the future for podocyte research. The main meeting over 3 days included a keynote talk and 4 focused sessions each day incorporating invited talks, followed by selected abstract presentations, and an open panel discussion. The conference concluded with a Patient Day, which brought together patients, clinicians, researchers, and industry representatives. The Patient Day was an interactive and diverse day. As well as updates on improving diagnosis and potential new therapies, the Patient Day included a PodoArt competition, exercise and cooking classes with practical nutrition advice, and inspirational stories from patients and family members. This review summarizes the exciting science presented during the 13th International Podocyte Conference and demonstrates the resilience of researchers during a global pandemic.

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The sections of this review follow the sequence of the conference sessions, which were paired with a basic science session, followed by a linked translational research session.

Cell-cell and cell-matrix signaling

Podocytes attach at specialized cell-cell junctions known as slit diaphragms and interact with the glomerular basement

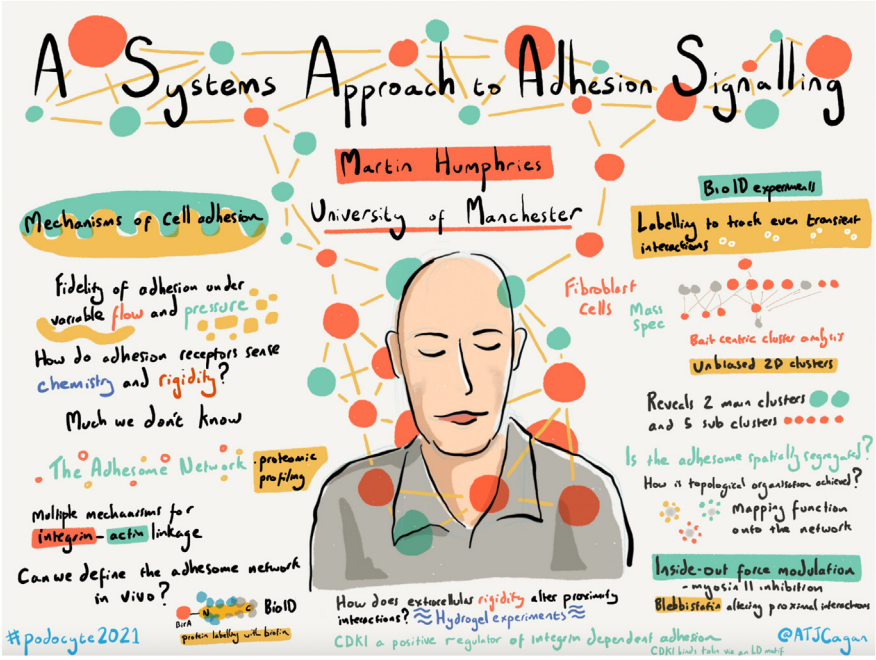

Figure 1 | A systems approach to adhesion signaling. Graphic illustration of the keynote talk from Martin Humphries; illustrated by Alex Cagan. BioID, proximity-dependent biotin identification; BirA, bifunctional ligase/repressor; CDK1, cyclin-dependent kinase 1.

membrane at the cell-matrix interface.[1] During a keynote talk, Martin Humphries gave insights into mechanisms of cell-matrix adhesion (Figure 1). Using predominantly fibroblast culture systems, his research group has defined the adhesome network[2] and used proximity labeling to study the potential interactions within this complex protein nexus.[3] This has identified topological associations between cell-matrix adhesion components, with 2 main clusters of proteins and 5 subclusters. These clusters correspond to the differing complexes of core proteins that constitute the consensus adhesome, which is the collective set of proteins that localize to focal adhesions. Surprisingly, the myosin II inhibitor blebbistatin or matrix rigidity did not have a significant impact on the spatial proximity of adhesion proteins but did have a major effect on actin-binding interactors. Connections between cell-matrix adhesion components and cell cycle proteins were also presented, with a novel role for cyclin-dependent kinase 1 as a positive regulator of focal adhesions.[4] Cyclin-dependent kinase 1 binds directly to the focal adhesion component talin1 leucine-aspartic acid motifs in the R8 domain[5] and is likely to control adhesion assembly and maintenance.

The first focused session continued the cell-matrix signaling theme and introduced cell-cell signaling in the context of glomerular pathology. Membranous nephropathy is an autoimmune disease with immune complexes deposited into the glomerular basement membrane. Mario Schiffer presented new insights into the pathogenesis of membranous nephropathy and the interplay of glomerular cells and the glomerular basement membrane. He described the application of microRNA (miR) screens to identify upregulation of 2 miRs in membranous nephropathy, which both target the basement membrane protein nephronectin and affect the permeability of the glomerular basement membrane for Igs. Increased miR-192 expression was detected specifically in endothelial cells on stress, suggesting that idiopathic membranous nephropathy could primarily be an endothelial cell disease.[6,7]

Britta George focused on the signaling crosstalk in podocytes between slit diaphragm proteins and focal adhesions and described a role for nephrin in the recruitment and activation of integrin β-1 at focal adhesion sites.[8] Moving to crosstalk between adhesions and the extracellular matrix, Christoph Schell highlighted a role for the podocyte-specific adhesion protein Erythrocyte Membrane Protein Band 4.1 Like 5 (EPB41L5) in the reinforcement of adhesion in response to physiological cues and the regulation of assembly of extracellular matrix proteins. He also highlighted that glomerular disease is associated with the hyperactivation of EPB41L5, increased mechanosensing, and disease progression.[9,10] Continuing the theme of mechanoregulation and addressing the long-standing question about the mechanisms of albuminuria, Thomas Benzing described a mouse model with compound heterozygous mutations in *Nphs2*, which allowed the focus on early stages of glomerular disease.[11] Using superresolution light microscopy, artificial intelligence, and modeling, this study revealed an inverse correlation of slit diaphragm length and albuminuria at early stages of glomerular disease. This observation supports a prior hypothesis that shortening of the slit diaphragm affects the hydraulic conductivity of the glomerular basement membrane, and compression of the basement membrane prevents

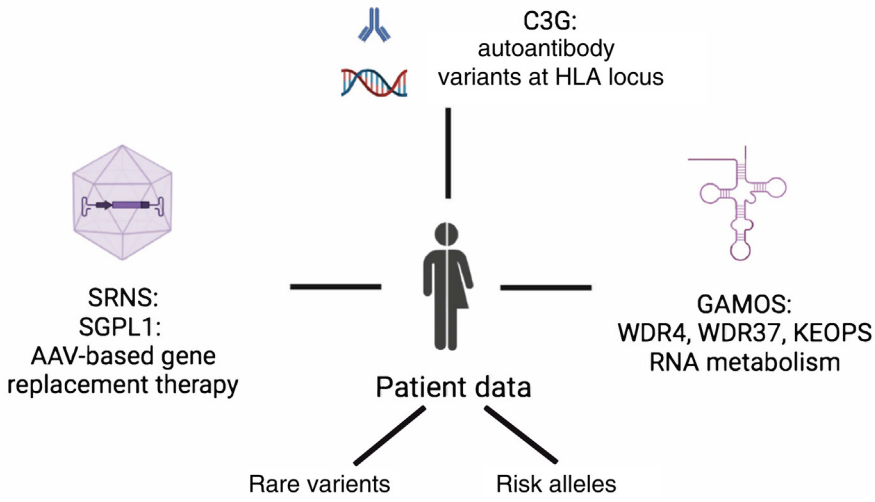

Figure 2 | Genetics from diagnosis to therapy. Examples of where genetic investigation is leading the way to improving diagnostic accuracy. AAV, antineutrophil cytoplasmic antibody–associated vasculitis; C3G, C3 glomerulopathy; GAMOS, Galloway-Mowat syndrome; HLA, human leukocyte antigen; KEOPS, Kinase, Endopeptidase and Other Proteins of small Size; SGPL1, Sphingosine-1-Phosphate Lyase 1; SRNS, steroid-resistant nephrotic syndrome; WDR, tRNA (guanine-N(7)-)-methyltransferase non-catalytic subunit WDR4.

albumin diffusion.[12] Benzing further added observations that suggest diseased podocytes apply decreased buttress force on the glomerular basement membrane, which, in turn, results in an increased permeability of the filtration barrier.[13] This is in agreement with previous work discovering the native structure of the slit diaphragm and showing that the slit diaphragm is nonrestrictive to albumin.[14] Overall, this study described the evolution of glomerular disease and highlighted the interplay between podocytes and the extracellular matrix contributing to the development of albuminuria.

Genetics from diagnosis to therapy

Another important route to therapy is targeting the disease origin through the identification of causative gene variants and their pathogenic function. Nephrotic syndrome is a clinical presentation associated with inherited kidney diseases affecting glomerular function. Matthew Sampson gave an overview of the genetic architecture of nephrotic syndrome and described several rare variants[15] and common risk alleles, including *APOL1*[16] and *NPHS1*.[17] Daniel Gale focused his talk on the advances made in the understanding of familial C3 glomerulopathy. Although C3 glomerulopathy is linked to monogenic variants in the complement-associated genes *CFH*, *C3*, and *CFHR*, some observations cannot be explained by the monogenic etiology. Using the National Registry of Rare Kidney Diseases based in the United Kingdom,[18] an increase in frequency of common variants at the human leukocyte antigen locus in primary membranoproliferative glomerulonephritis was detected, suggesting that C3 glomerulopathy may be an autoimmune disorder.[18]

Moving to a rare cause of nephrotic syndrome, Corinne Antignac reported recent findings in Galloway-Mowat syndrome. Although 11 different genes have been identified as affected in Galloway-Mowat syndrome, most patients present with variants in the genes encoding *WDR4*,[19] *WDR73*,[20] and the Kinase, Endopeptidase and Other Proteins of small Size (KEOPS) complex.[21,22] All of these genes are involved in RNA metabolism, which could therefore serve as a targetable pathway. Using different *in vitro* and *in vivo* models of the respective patient variants will help to further unravel disease mechanisms in Galloway-Mowat syndrome.[21,22] Describing another rare glomerular disorder, steroid-resistant nephrotic syndrome (SRNS), Friedhelm Hildebrandt reported a novel *ADCK4* mutation and identified a role for aarF domain containing kinase 4 (ADCK4) in coenzyme Q_{10} biosynthesis. Food supplementation of coenzyme Q_{10}[23] showed a beneficial effect on *ADCK4*-associated SRNS. However, the broad genetic heterogeneity, with 59 monogenic causes for SRNS described to date, renders the development of novel drugs for each target difficult. Therefore, a modifiable gene replacement platform could be a paradigm shift in treating SRNS.[24,25] Overall, this session highlighted that the significant advances in genetics and genomics are leading the way to improving diagnostic accuracy (Figure 2).

Understanding basement membranes

In addition to genetic variants affecting intracellular and cell surface podocyte components, variants in basement membrane genes have also been associated with glomerular phenotypes, including focal segmental glomerular sclerosis (FSGS). Analysis of data from next-generation sequencing studies has revealed that variants in *COL4A* basement membrane genes are more common in glomerular disease phenotypes. Therefore, improving understanding of the composition, cell-matrix interactions, and dynamics of the glomerular basement membrane is important, and necessary, for the development of new therapies.

The study of basement membrane dynamics is challenging, and there are many unanswered questions about protein turnover and the capacity for basement membrane repair.

David Sherwood presented a basement membrane tagging approach in *Caenorhabditis elegans*, which has facilitated the study of linkage between adjacent basement membranes. He described a crucial structural role for type IV collagen in maintaining the linkage between 2 basement membranes that link during gonadal development in *C elegans*.[26,27] Many of the core basement membrane components present in mouse and human basement membranes are conserved in *C elegans* and, therefore, insights from this system could improve understanding of basement membrane regulation and dynamics in vertebrates. The role of type IV collagen is compromised in Alport syndrome, and this may result in weakened linkage between adjacent podocyte and endothelial basement membranes in the glomerulus. Indeed, the characteristic splitting of the glomerular basement membrane gives the appearance of 2 distinct basement membranes as opposed to 1 uniform basement membrane in healthy tissue.

In addition to core basement membrane collagens and laminins, there are many other minor basement membrane components in the glomerulus, including nephronectin. Denise Marciano demonstrated a role for nephronectin in glomerular development and showed its deposition into the basement membrane by mesangial cells. Further characterization demonstrated that nephronectin interacts with cells via integrin $\alpha 8\beta 1$ and is required for normal glomerular development.[28] The importance of nephronectin in glomerular development is highlighted by the recent findings of a biallelic frameshift variant in *NPNT* causing bilateral kidney agenesis in patients.[29] From investigating the function of basement membrane components, high-resolution imaging is improving understanding about the spatial arrangement of glomerular basement membrane components. Hani Suleiman described the use of superresolution microscopy techniques[30] to map basement membrane molecules in human samples in health and disease. Having established a crucial role for basement membrane components for glomerular development and in disease, Jeffrey Miner asked the question, "Can we repair the glomerular basement membrane?" Alport syndrome is caused by variants in the type IV collagen genes *COL4A3*, *COL4A4*, and *COL4A5*, and no drugs so far target their repair.[31] New emerging tools, such as gene therapies, nonsense variant readthrough, and protein therapies, were discussed. In this context, it appears also interesting that recently prolyl 3-hydroxylase 2 (P3H2), a podocyte-expressed collagen IV modifier, was identified as a potential novel drug target.[32]

Podocyte pathology

Glomerular diseases are often caused by variants in podocyte-specific genes, such as *NPHS1*,[33] *NPHS2*,[34] *COL4A*[3–5,35] and *LAMB2*.[36] However, nonpodocyte genetic variants also cause kidney disease. Apolipoprotein L1 (APOL1) is primarily expressed in the innate immune system, and no role for APOL1 in kidney function has been identified to date. Yet, APOL1 gene variants are associated with kidney disease.[37] Martin Pollak described the development of mouse models carrying different *APOL1* gene variants that are highly associated with proteinuric kidney disease. Upregulation of systemic interferon-γ resulted in upregulation of APOL1 and induced proteinuria in pathogenic APOL1 variant mice. Expression of mixed allele variants revealed that zygosity influences the severity of kidney disease.[38]

Diabetes is a well-known risk factor for kidney disease. To uncover novel targets in diabetic nephropathy, Agnes Fogo used glomerular RNA-sequencing data from the db/db endothelial nitric oxide synthase$^{-/-}$ mouse model and human biopsies and demonstrated dishevelled associated activator of morphogenesis 2 (DAAM2) upregulation in diabetic nephropathy. Experiments in primary podocytes indicated a DAAM2-mediated regulation of mammalian target of rapamycin and Wnt/β-catenin signaling pathways.[39] Highlighting the descriptive nature of FSGS, Moumita Barua described the importance of identifying new genetic and pathologic biomarkers in FSGS. Performing whole exome sequencing in patients with FSGS, she identified 20% of individuals carrying a pathogenic or likely pathogenic variant, most frequently in genes that encode for *COL4A3/4/5* or podocyte-specific proteins.[40]

Stuart Shankland concluded this focused session and was presented with the Marylin Farquhar award for considerable contribution to kidney research. In his presentation, he focused on the pathologic effect of aging on podocytes. Performing bulk RNA sequencing on isolated podocytes from young and aged mice revealed an increase in immune response signaling pathways, gene silencing, and mitogen-activated protein kinase signaling in aged podocytes.[41,42] Further investigation of the intersection between aged and injured podocytes may well unravel new potential targets for therapy.

Glomerular crosstalk

Crosstalk between the different glomerular components influences glomerular function, and dysregulation of one component can affect others. For example, the shortening of slit diaphragm is associated with decreased buttress force application on the glomerular basement membrane, ultimately resulting in the development of albuminuria. Filtering the blood, the glomerular filtration barrier is exposed to mechanical load, which requires the glomerulus to sense and adapt to mechanical cues. To study podocyte response to mechanical stress, Nicole Endlich subjected podocytes to biaxial cyclic stretch using a custom-built apparatus and found actin cytoskeletal rearrangements and regulation of αv-integrin adhesions.[43] Specifically, she identified roles for adhesion and actin-associated protein integrins,[44] fascin-1 and filamin A,[45] as stress-responsive proteins in podocytes and furthermore for the matrix proteins osteopontin[46] and fibronectin,[47] indicating stress-induced regulation of extracellular matrix in podocytes.

With a dominance of podocyte and basement membrane research presented during the conference, Rebecca Foster

emphasized the importance of glomerular endothelial cells and their glycocalyx as an effective primary barrier against protein loss.[48] In paracrine signaling, for example, between podocyte and endothelial cells, proteins such as vascular endothelial growth factor A/C,[49] angiopoietin-1,[50,51] and heparanase regulate the endothelial glycocalyx, and could be used to develop novel therapeutic approaches to target glomerular diseases. Marcus Möller followed by describing the role of parietal epithelial cells (PECs) in the pathogenesis of glomerular disease. Although FSGS has been described as a passive sclerosing process, he demonstrated that PECs actively contribute to the formation of sclerotic lesions by migrating and invading into the area of the primary insult or podocyte damage and could serve as a potential pharmacologic target.[52,53] The glucocorticoid cortisone deactivated PECs and prevented the formation of sclerotic lesions. He further presented data on a new cell subtype, intermediate PECs, which are located between flat PECs, lining Bowman's capsule, and cuboidal PECs[54] and contribute to tip lesion formation in FSGS.

Continuing the PEC theme and their role in sclerotic lesion formation in glomerular disease, Pierre-Louis Tharaux described the discovery that inactivation of an essential gene for PEC activation, Cluster of Differentiation 9, also prevents lesion formation in glomerular disease. *De novo* expression of Cluster of Differentiation 9 in PECs is a common pathogenic switch driving glomerular injury in crescentic glomerulonephritis and FSGS in human and mice.[55] He highlighted the importance of crosstalk between podocytes, GECs, and PECs as injured podocytes and altered endothelial cells activate PECs, trigger extracapillary lesions, and lead to FSGS.[56]

Immune-mediated glomerular diseases

Immune-mediated glomerular diseases are a major cause of end-stage kidney disease. Although the underlying mechanisms remain largely unknown, in autoimmune glomerular disease, there have been major advances in the identification of autoantigens. Performing laser microdissection of patient samples and mass spectrometry–based proteomics, Pierre Ronco presented the discovery of exostosin, neural cell adhesion molecule 1 (NCAM1), neural epidermal growth factor-like 1 protein (NELL1), semaphorin 3B, protocadherin 7 (PCDH7), and contactin-1 as novel antigens associated with membranous nephropathy.[57,58] With only the increasing identification of antigens, he emphasized that analysis of commonalities in the pathobiology will be crucial for classification, therapy, and the prediction of prognosis.

IgA nephropathy presents as the most common primary glomerulonephritis. Jonathan Barratt gave an update on ongoing studies and promising novel therapeutics. He focused on the NefIgArd study with NEFECON,[59] which is a novel oral formulation of the steroid budesonide. At the end of 2021, this was granted accelerated approval by the US Food and Drug Administration to reduce proteinuria in IgA nephropathy. The uses of eculizumab, which targets C5 of the complement system,[60] and narsoplimab, which targets mannan-associated lectin-binding serine protease-2 (MASP-2),[61] were also described as potential therapies for IgA nephropathy. Marina Noris discussed new work defining additional subclasses of immune complex–mediated C3 glomerulopathy, which could help with predicting therapy responsiveness. Turning to a rare autoimmune disease, Silke Brix presented data on the role of factor H in antineutrophil cytoplasmic antibody–associated vasculitis. Factor H–related proteins are potentially involved in early stages of glomerular injury in antineutrophil cytoplasmic antibody–associated vasculitis, and crescent formation by PECs might be a potential therapeutic target. Furthermore, she highlighted the potential for the integration of deep learning–based podometrics in antineutrophil cytoplasmic antibody–associated vasculitis into the clinical setting.[62]

Experimental models

Having access to whole genome databases and patient cohort data sets has led to the identification of new antigens and disease-associated gene variants. To develop relevant new therapeutics requires suitable systems to study their function and relevance in disease. In this session, the advantages and disadvantages of multiple experimental models (mice, zebrafish, *C elegans*, and kidney organoids) were discussed in reference to their suitability for podocyte research. A consensus was achieved, with the panel highlighting the experimental model used should be dependent on the research question posed. The panel also highlighted collaboration and the use of multiple models as important to successful outcomes in animal and organoid research.

In a keynote talk, Melissa Little focused on kidney organoids as a model of the developing human kidney (Figure 3). Kidney organoids contain accurately patterned glomeruli with polarized slit diaphragm proteins and maturing glomerular basement membrane components.[63] Single-cell profiling of kidney organoids revealed robust and reproducible component cell types with strong congruence to human fetal kidney.[64] Combining with Clustered regularly interspaced short palindromic repeats–CRISPR-associated protein 9 (CRISPR-Cas9) genome editing, a series of reporter cell lines, mutated cell lines, and corrected patient cell lines have been generated, and differentiated into kidney organoids to model known podocytopathies, validate genetic variants, and screen for new treatments.[63,65,66] Despite the advantages of kidney organoids, several challenges remain in the field, including limited functional maturation and a nonphysiological environment with no blood supply or urine flow. Further optimization of the differentiation protocol *in vitro* and transplantation *in vivo* may improve vascularization and maturation and therefore enhance the capacity to use organoids to study glomerular disease.

Susan Quaggin introduced the use of mouse models and described investigation of Nck adaptor proteins, which link nephrin and podocin to the actin cytoskeleton, as an example of the benefits of using the mouse to model glomerular disease.[67,68] Mira Krendal followed with her investigations into *Myo1e* in mice and with complementary *in vitro* models,

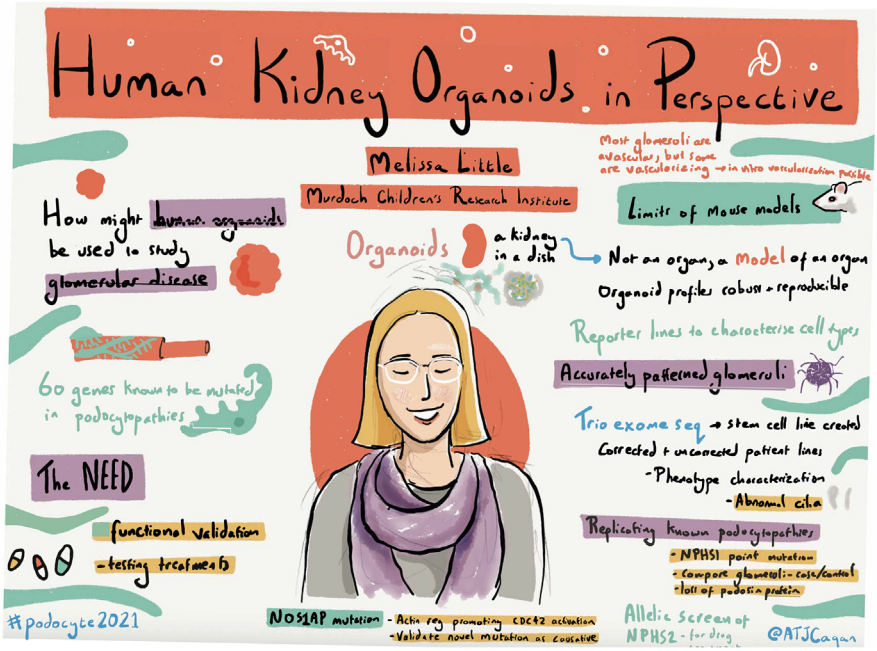

Figure 3| Human kidney organoids in perspective. Graphic illustration of the keynote talk from Melissa Little; illustrated by Alex Cagan. NOS1AP, nitric oxide synthase 1 adaptor protein; NPHS1, nephrin.

highlighting many insights into the role of this protein in slit diaphragm junctions.[69] This included specific defects in *Myo1e* that affect its localization to slit diaphragm junctions and its dissociation from this junction.

The impact of genetic heterogeneity on the interpretation of animal models was highlighted by Ron Korstanje, who has developed a genetic diversity model by outcrossing 8 different strains of mice. Crossing this model to a *Col4a5* knockout (Alport) mouse demonstrated diverse responses to the Alport phenotypes. Genetic modifiers were uncovered that determine the severity of the disease features, including the *Fmn1*, which encodes a protein involved in the formation of adherens junctions and the polymerization actin.[70] Daniel Shaye followed, describing how *FMN1* orthologues in *C elegans* can be used to study tubulogenesis and provide insights into the role of formins in FSGS. The *C elegans* excretory cell generates remarkable cellular protrusions that create canals spanning almost the full length of the worm. Disease-associated variants in *FMN1* caused constitutive activity affecting the dynamics of microtubules, which may be relevant to the disease mechanism associated with *INF2* variants in FSGS.[71] Benjamin Freedman concluded this focused session by describing the use of kidney organoids to investigate APOL1-associated nephropathy, which is difficult to model in nonhuman experimental systems and hence the requirement for a human experimental model.[72] Overall, there is now a rich toolkit of complementary experimental systems to investigate the underlying mechanisms of glomerular disease.

Drug development

If untreated, chronic kidney disease (CKD) can progress into kidney failure. State-of-the-art treatment targets the workload of the kidneys, extending their survival. However, disease progression often cannot be avoided, highlighting the urgent need for better and more specific drugs. Andrey Shaw opened this focused session by highlighting the challenges of developing new drugs for kidney disease. First, many diagnostic categories and pathologic descriptors make it difficult to define the various subtypes of disease within the CKD spectrum. Second, diagnostic tools are still poor and mainly rely on clinical features elicited from the history and physical examination, together with basic blood and urine investigations. This emphasizes the need to identify more specific blood and urine biomarkers. Moreover, designing clinical trials is difficult, and the development of novel drugs is challenging, as they need to be superior to established drugs as those that inhibit the renin-angiotensin-aldosterone system.

Aliza Thompson, from the US Food and Drug Administration, explained the requirements and challenges for trial design and realization. She highlighted the need for a global process based on worldwide patient data and discussed the different approval pathways and the definition of study end points. Finally, she emphasized that trial design should be modified to improve the experience of participants and trial outcomes. Matthew Breyer gave an update on studies using a sodium-glucose co-transporter-2 inhibitor for treating diabetic kidney disease (DKD).[73,74] He presented a novel mouse model recapitulating human DKD by inducing hypertension in diabetic mice via adeno-associated virus delivery of renin.[75,76] This model does not only present with hallmarks of DKD, but also responds to treatments used in the clinic.[75,76] At present, mainly animal models are used during preclinical studies, although the translatability to the human

condition remains unclear. Peter Mundel presented the advantages of using transplanted and perfused human kidney organoids for testing new drugs.[77] Studies using GFB-887, a human Short transient receptor potential channel 5 (TRPC5) inhibitor, showed a protective effect during protamine sulfate-induced podocyte injury after oral delivery in rats with transplanted human organoids.[77]

Podocytes in multisystem regulation and disease

As the glomerulus filters the blood, glomerular cells are exposed to soluble factors, and they release proteins into the circulation. This multisystemic crosstalk affects kidney, and the function of remote organs and tissues can be affected. Tobias B. Huber focused on the crosstalk between the glomerulus and skeletal muscle. Muscle wasting is often detected in advanced CKD.[65] He described the discovery that activin A, which is secreted from cells of mesangial origin, was increased in mice and humans with CKD, and the increase caused a reduction in protein synthesis in skeletal muscle. Sequestering activin A in the serum of CKD mice or the downregulation of its receptor prevented muscle loss, which raises the question of whether this pathway could be exploited to prevent muscle wasting in patients with advanced CKD.[78,79] CKD can develop secondary to systemic disease. One example is DKD, where sustained high blood glucose levels damage the kidney. Richard Coward studies molecular signaling in DKD.[80] Podocytes are sensitive to insulin,[81] and a recent study identified reduced glomerular expression of insulin-like growth factor–binding protein-1 in diabetes, suggesting the preservation of insulin-like growth factor–binding protein-1 in diabetes as a potential therapeutic route.[82] In this session, Richard gave insights into the pathobiology of hemolytic uremic syndrome. Hemolytic uremic syndrome is induced through the release of Shiga toxin by *Escherichia coli*, which binds to kidney cells via the cell membrane protein globotriaosylceramide[83] and promotes podocyte injury.[84] Globotriaosylceramide also plays a role in Fabry disease, which is another systemic disorder. Although accumulation of globotriaosylceramide in lysosomes has been considered the major pathologic factor in Fabry disease,[85] Fabian Braun illustrated a globotriaosylceramide-independent accumulation of pathogenic synuclein α in Fabry podocytes.[86] Finally, Fabiola Terzi investigated the effect of aging on glomerular signaling and showed that aging-associated signaling from plasminogen activator inhibitor type 1 (PAI-1)–positive senescent endothelial cells contributes to podocyte loss and glomerular scarring.[87] Both PAI-1 inhibition and senolysis rescued podocyte numbers in aging mice, and PAI-1 expression was found as a predictor of kidney transplant survival.

Next-generation phenotyping

A variety of novel tools and techniques can now provide the opportunity to delineate complex mechanisms and identify new players in CKD. In this focused session, 4 examples were given of how the integration of data from *in vitro* and *in vivo* models with patient phenotype data and multiomic analysis is helping to better understand CKD. Markus Rinschen combines proteomics and metabolomics to define the molecular identity of podocytes in different disease setting. This approach of functional proteomics does not only measure protein levels, but also aims to characterize the functional role of proteins, their interaction partners, and posttranslational modifications under physiological and stress conditions.[88–95] Several variants in mitochondrial genes, such as *PDSS2*, *CoQ6*, and *ADCK4*,[9] are described to be causative for SRNS, emphasizing the important role of mitochondria for podocyte biology. Paul Brinkkoetter investigated their function in podocytes and in particular their role as key signaling hub in the cell.[76–78] Disruption of mitochondrial DNA transcription and loss of mitochondrial scaffold proteins revealed that, under physiological conditions, podocytes do not rely on mitochondrial energy supply.[96–98] Interestingly, dysfunctional mitochondria cause mammalian target of rapamycin hyperactivation via the insulin signaling cascade.[97] Many glomerular disorders are associated with the overproduction of extracellular matrix, a characteristic feature of organ fibrosis. Rafael Kramann identified the origin of myofibroblasts in kidney fibrosis.[79] Single-cell RNA sequencing coupled with advanced bioinformatic analysis revealed that myofibroblasts derive from pericytes and 2 distinct fibroblast subsets. Furthermore, he presented naked (NKD) inhibitor of WNT signaling pathway 2 as a potential target in antifibrotic therapy.[99] Moin Saleem explained how to identify phenotypic signatures from big patient cohort data sets and how to address the challenges of heterogeneity in nephrotic syndrome. Reclassifying idiopathic nephrotic syndrome based on "single gene disorders," "circulating factor disease," and "other mechanisms" will help to understand underlying mechanisms and to develop specific treatments.[100] Furthermore, molecular phenotyping can help to separate the different disease types by administering patient plasma to *in vitro* models[101,102] and by performing large-scale epigenetic screening.

Identifying new disease pathways

The application of single-cell RNA sequencing (scRNAseq) has transformed understanding about kidney development and disease. In a keynote talk, Menna Clatworthy presented the use of scRNAseq to define cell types in the human kidney (Figure 4). Two-photon microscopy, bulk RNA sequencing, and fluorescently activated cell sorting experiments demonstrated that the kidney is packed with macrophages as well as a compartment-specific distribution of mononuclear phagocytes and chemokines.[103] Although fluorescently activated cell sorting is commonly used to identify immune cells and specific cell subtypes in tissues, fluorescently activated cell sorting requires prior knowledge about cell markers, has the associated difficulties of identifying cell heterogeneity, and does not inform about cellular origins of transcripts. To overcome these limitations, droplet barcoding scRNAseq[104] characterized cell types in the human kidney at different developmental stages.[105] Having a focus on immune cells, adaptive B and T

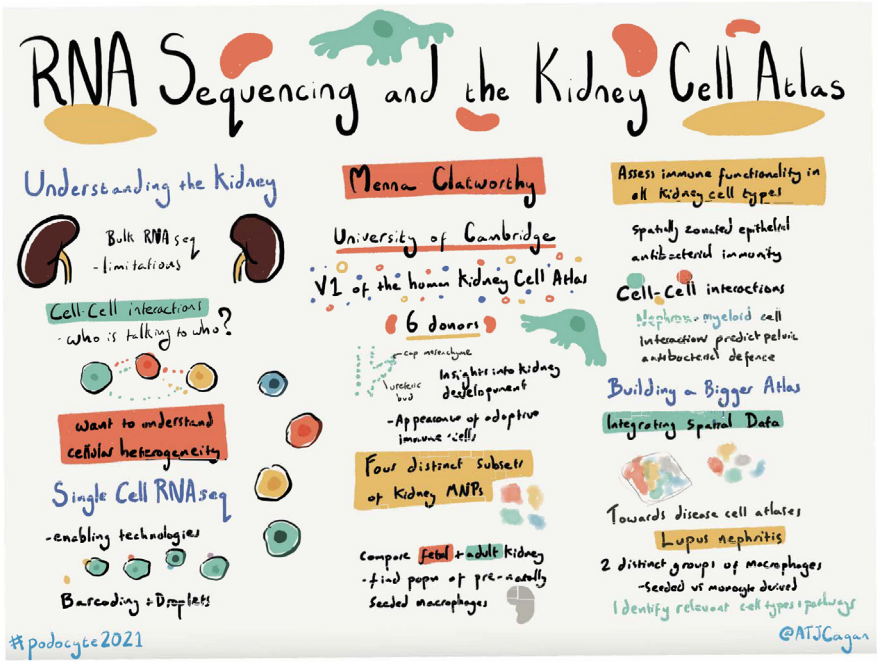

Figure 4| RNA sequencing and the kidney cell atlas. Graphic illustration of the keynote talk from Menna Clatworthy; illustrated by Alex Cagan. MNP, mononuclear phagocyte; RNAseq, RNA sequencing.

immune cells were found in prenatal kidney samples. scRNAseq enabled the identification of adult kidney macrophages as being seeded already in the embryonic kidney and identified macrophage subtypes with different capability for phagocytosis. More important, the data from these studies are curated in kidneycellatlas.org, which will incorporate disease-associated scRNAseq data in the future.

New technical advances help to uncover complex cellular pathways and their cell type–specific regulation in health and disease. Katalin Susztak described how genome-wide association studies can be combined with single-cell transcriptomics[106] to link genetic variants to cellular populations, cell-specific expression, and even epigenomic regulation.[107–109] Recently, her group combined expression quantitative trait loci data analysis with scRNAseq and assay for transposase-accessible chromatin with high-throughput sequencing (ATACseq) and identified specific cell populations affecting kidney function and blood pressure.[110] Metabolic memory describes a positive long-term effect on diabetic complications on immediate intensive treatment of hyperglycemia. The underlying mechanisms of this effect are still poorly understood. Rama Natarajan and her team identified differently methylated DNA loci in white blood cells, indicating a role for epigenetic regulation in metabolic memory. In detail, insufficient glycemic control leads to changes in methylation of, for example, the 3' untranslated region of Thioredoxin-interacting protein (TXNIP), which is a pro-oxidant associated with podocyte damage.[111,112] These data indicate that diabetes leaves the chromatin open and accessible for modification and to facilitate metabolic memory.[113]

To investigate the molecular changes in transplanted kidneys undergoing antibody-mediated rejection, acute cellular rejection, or acute tubular necrosis, Ana Konvalinka described the use of mass spectrometry–based proteomics of laser microdissected glomeruli and the tubulointerstitium.[114] Her team identified the downregulation of focal adhesion, podocyte, and extracellular matrix proteins, indicating matrix remodeling as an early sign of antibody-mediated rejection.[114] Jochen Reiser gave an update on soluble urokinase-type plasminogen activator receptor and its role in kidney disease. Soluble urokinase-type plasminogen activator receptor is an immune-derived, circulating factor and, in some studies, was found to be upregulated in kidney and cardiovascular diseases.[115–118] More recently, the identification of murine soluble urokinase-type plasminogen activator receptor 2 was found to form a stable dimer and to cause kidney damage similar to FSGS.[119] Overall, this session highlighted the wide range of pathways that are perturbed in glomerular disease and the experimental approaches in use to harness this disease complexity.

The new therapy horizon

Great advances have been made in the field of podocyte research in the last years, which build the foundation for developing new therapies. The closing session of the 13th International Podocyte Conference gave insights into the new directions of targeted therapy for glomerular disease.

Targeting the perturbed lipid homeostasis of podocytes in glomerular disease, Alessia Fornoni presented data on the characterization of 5-arylnicotinamide. Specifically, this compound induces a transporter for free cholesterol, ATP-binding cassette A1 (ABCA1), resulting in increased cholesterol efflux in podocytes and improved survival in a mouse model of Alport

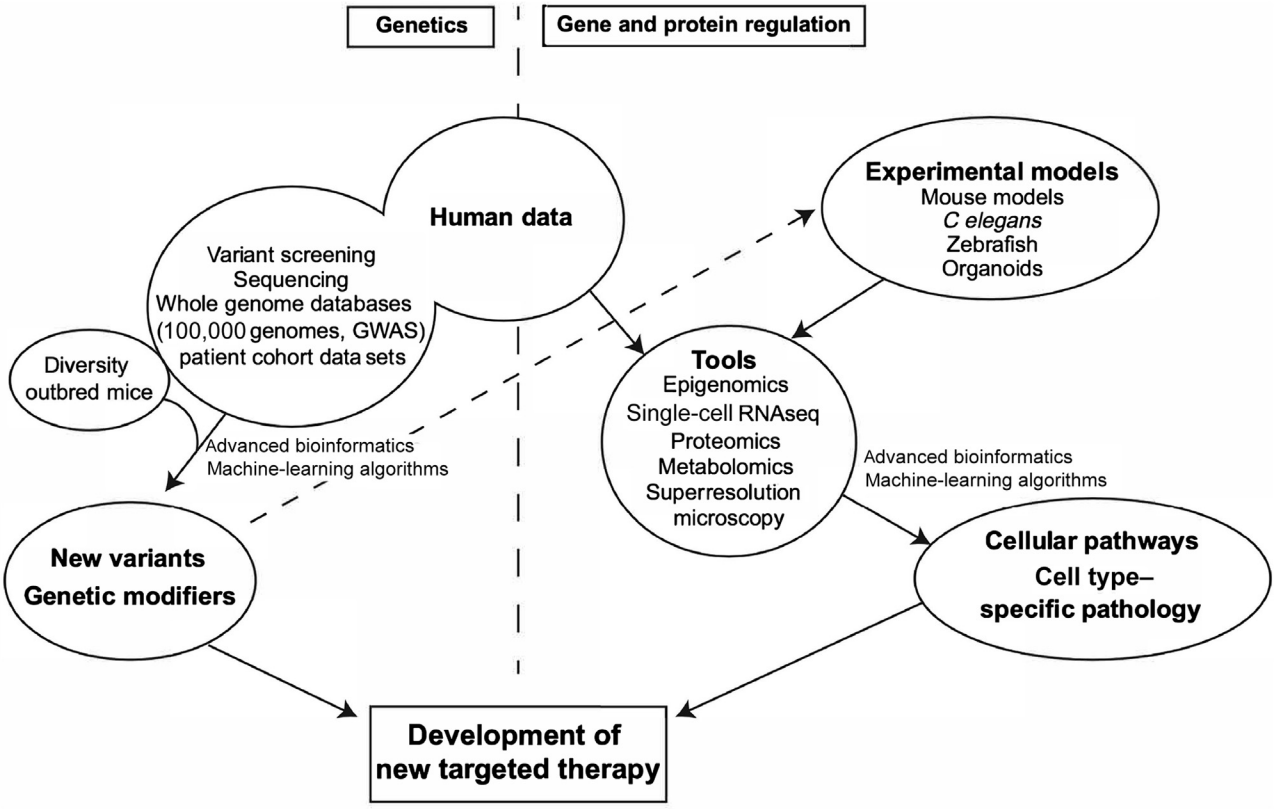

Figure 5 | Advances made in podocyte research. Access to human database and patient cohort data sets allows the identification of new gene variants. A diverse set of experimental models, access to patient samples, and the use of advancing techniques, such as -omics and single-cell RNA seq (RNA sequencing), elucidate cell type–specific pathologies and cellular pathways. Increasing understanding of the molecular mechanisms in glomerular diseases is leading to the development of new targeted therapies. *C elegans*, *Caenorhabditis elegans*; GWAS, genome-wide association study.

syndrome and FSGS.[120] Also targeting the lipid metabolism pathway, Joshua Zaritsky showed that lipid apheresis was effective in treating steroid-resistant FSGS by adsorbing very low-density lipoprotein and low-density lipoprotein.[121] Although FSGS often reoccurs post-transplantation, 7 of 11 patients went into remission on lipid apheresis treatment. Ongoing trials and analysis of serum composition before and after apheresis will give a clearer view about the mechanism in the future. Current treatments for SRNS include immunosuppressive therapy, angiotensin-converting enzyme inhibitors, and coenzyme Q_{10} supplementation. Anna Greka showed new directions in treating coenzyme Q deficiency-associated SRNS by targeting serine/threonine-protein kinase B-raf (BRAF)/mitogen-activated protein kinase pathways and reversing polyunsaturated fatty acid–associated lipid peroxidation *in vivo*.[122] Matthias Kretzler presented a patient-directed approach to identify druggable pathways in nephrotic syndrome. He described prospective cohort studies and machine-learning algorithms for the discovery of disease-specific molecular pathways and multiscalar outcome prediction of disease, based on clinical data, transcriptomic data, weighted gene coexpression network analysis, and demographic and pathology data. Tumor necrosis factor was identified as a potential target[123] and validated in kidney organoids and in an enzyme-linked immunosorbent assay for urinary biomarkers as noninvasive surrogates of tumor necrosis factor activation.

Summary

This review highlights the advances made in glomerular research and presented at the 13th International Podocyte Conference (Figure 5). Advances have been made in the identification of disease-causing gene variants and in the understanding of disease mechanisms and affected pathways. Access to new techniques, such as scRNAseq, provided new insights into the crosstalk between glomerular cells and other tissues. Finally, new, and constantly improving, experimental models help to develop innovative and more targeted therapies for disease associated with the podocyte. The conference talks were all illustrated by Alex Cagan (Figures 1, 3, and 4 and Supplementary Figures). These summary illustrations were an effective means of live content dissemination during the conference and are an important record of this dynamic meeting.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Figures. The complete set of illustrated talks from the 13th International Podocyte Conference.

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