Targeting the Kidneys at the Nanoscale: Nanotechnology in Nephrology

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Kidney diseases, both acute and chronic, are a substantial burden on individual and public health, and they continue to increase in frequency. Despite this and an intense focus on the study of disease mechanisms, few new therapeutic approaches have extended to the clinic. This is in part due to poor pharmacology of many, if not most, therapeutics with respect to the sites of kidney disease within the glomerulus or nephron. Considering this, within the past decade, and more pointedly over the past 2 years, there have been substantial developments in nanoparticle systems to deliver therapeutics to the sites of kidney disease. Here, we provide a broad overview of the various classes of nanomaterials that have been developed to improve therapeutic development for kidney diseases, the strategy used to provide kidney accumulation, and briefly the disease models they focused on, if any. We then focus on one specific system, polymeric mesoscale nanoparticles, which has broadly been used over 13 publications, demonstrating targeting of the tubular epithelium with 26-fold specificity compared with other organs. While there have been several nanomedicines that have advanced to the clinic in the past several decades, including mRNA-based coronavirus disease vaccines and others, none have focused on kidney diseases specifically. In total, we are confident that the rapid advancement of nanoscale-based kidney targeting and a concerted focus by clinicians, scientists, engineers, and other stakeholders will push one or more of these technologies into clinical trials over the next decade.

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Introduction

Kidney Disease Therapies

Kidney diseases, both acute and chronic, are major and growing health burdens worldwide as risk factors, such as diabetes and hypertension, become more prevalent.[1–3] AKI can arise from various etiologies, including chemotherapeutics or antibiotics, sepsis, ischemia, or others, and occurs in up to 67% of critically ill patients.[4,5] CKD is hallmarked by glomerular and/or tubular fibrosis and progressive dysfunction, with causes ranging from diabetes, hypertension, or others, and it affects up to 10% of the population.[6] In both AKI and CKD, depending on the severity, etiology, and baseline reserve, progression to ESKD can occur.

Therapeutics for both AKI and CKD are limited. ESKD is typically only manageable through RRT—dialysis or kidney transplant.[7] There are no optimal pharmacologic interventions to prevent AKI or progression of CKD.[7] BP control, management of underlying conditions such as diabetes, and avoidance of nephrotoxic drugs are key to avoid CKD progression. Renin angiotensin aldosterone system blockade, including angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, as well as sodium–glucose cotransporter-2 blockade, slow kidney disease progression but no treatment has consistently reversed kidney injury.[8–10] However, in many cases, these therapies fail to directly address underlying renal tissue damage and reverse progression of kidney dysfunction.[11] There have been many clinical trials of potential pharmacologic agents to treat AKI or CKD; however, none have proven highly effective and safe in patient populations. This is in part due to a historical lack of strong therapeutic target identification, which is the subject of intense ongoing study. It is further due to difficulty in targeting effective therapies directly to the site of kidney damage,[7] as normal kidney function is in opposition to typical drug uptake.

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Nanomedicine

Nanomedicine is the development of clinically translational diagnostic or therapeutic engineered materials with at least one dimension on the nanoscale (1–1000 nm).[12,13] One of the most prominent applications of nanomedicine is in drug and gene delivery, as these materials possess unique properties allowing them to improve pharmacologic characteristics of encapsulated therapeutics. Nanocarriers can be used to solubilize poorly water-soluble therapeutics and to achieve controlled drug release, resulting in lower frequency of dosing and increased patient compliance. Nanoparticles (NPs) are also able to preserve the integrity of easily degradable cargoes, such as biologics. Finally, in some circumstances nanomedicine enables drug targeting to specific organs and tissues, thus increasing drug concentration at a disease site, improving its efficacy, and reducing adverse effects in healthy tissues.[14,15]

Nanomedicines entered the pharmaceutical market almost three decades ago with the US Food and Drug Administration (FDA) approval of Doxil—the first NP therapeutic for cancer treatment.[16] Since then, 30 other NP drugs have reached the clinic in the United States and Europe, and over 70 therapeutics are currently being investigated in clinical trials.[17] NPs are used for various indications, including cancer therapies, iron replacement, fungal infections, macular degeneration, genetic liver disorders, and as imaging agents.[17–19] The most recent breakthrough in the nanomedicine field was the development of lipid NP mRNA vaccines.[20] Lipid NP delivery of unstable mRNA protects the mRNA molecule, thus allowing cell uptake and preventing immune responses.[21–24] Undoubtedly, coronavirus disease 2019 NP vaccines have made a major effect on global health care, but they also advanced the possibility of clinical translation of other NP drug delivery systems by establishing their safety for use in wide populations and demonstrating efficacy in delivering advanced molecular therapeutics.[25] Thus, the field of nanomedicine holds great promise for enabling the implementation of next-generation therapies and addressing previously unmet health care needs.

Those nanomaterials described above are made of lipid NPs,[26,27] although there are several other broad categories of materials. Indeed, there are other FDA-approved nanomedicines on the basis of polymeric materials, proteins, and inorganic NPs.[28] Iron oxide NPs have been widely used as iron-replaced therapies in anemic patients with CKD, with examples such as ferumoxytol and others.[29,30] This is largely because colloidal nanoscale iron oxide is more stable than other means of administration. In addition, while those examples above are primarily therapeutic or prophylactic in nature, nanomaterials are widely used in the clinic for imaging and diagnostic examples. One common use of nanotechnology in a diagnostic application is to provide contrast (the "pink color") in rapid coronavirus disease antigen tests or at-home pregnancy tests—which is achieved by gold nanoscale particles in a laminar flow immunoassay.[31,32] In each case, the specific material choice is important as it may be fine-tuned for the expected function and safety, such as the cargo used and the specific disease indication.

Here, we broadly outlined the current state of the literature on the development of nanotechnologies for kidney diseases. By and large, these have been evaluated in rodent models of disease, and we were excited to see an explosion of new technologies and papers over just the past 2 years. We are confident that this burgeoning interest and ongoing preclinical successes will eventually translate to patient-centered therapeutic and diagnostic development.

Development of New NP Systems That Target the Kidneys is Growing

With the increasing prevalence of kidney diseases, NP-targeted kidney delivery presents a promising approach to improve the pharmacology of therapeutics with respect to the kidneys. Given these benefits, kidney-targeted drug delivery systems have gained interest from numerous research groups and have been covered in a number of review articles. Several papers have reviewed kidney-targeted treatments used for particular kidney conditions, including various etiologies of AKI and CKD, renal cell carcinoma, renal fibrosis, and other kidney diseases.[33–41] Another group of review articles has focused on nanomedicines targeting different parts of the nephron,[42,43] specific cell types,[37,39,44,45] and subcellular localization.[44] Kidney targeting has also been described in relation to different drug carrier types, such as antibody conjugates, small molecule prodrugs, protein and peptide carriers, polymeric carriers, and NPs.[37,43,46] For NP-based kidney treatments, passive and active targeting mechanisms have been detailed.[39,44,47] Furthermore, a number of reviews have compiled the physicochemical properties of NPs that lead to kidney targeting, including the effect of size, shape, surface charge, composition, and surface modifications.[39,41,46–49] Thus, a growing body of literature on kidney-targeted drug delivery systems suggests the increasing importance of this approach in kidney disease management.

Given the recognized importance of kidney diseases and the substantial lack of therapeutic options for them, there has been a rapid increase in the number of novel NP systems designed to treat them. We performed a substantial literature search to identify these systems, finding publications primarily in materials and nanotechnology-based journals, with few disease-focused contexts (Table 1). Our search may have missed several published systems and therefore is likely not comprehensive, but any exclusions are unintentional. While we found a few systems (approximately five) which were published before 2015, the broad majority of publications we found were published within the past 2 years. Indeed, of the 35 particle systems in Table 1, 66% were published in 2021–2023. We outlined NP systems which the authors primarily described as kidney-targeted or that were used for kidney disease therapy. We should note, however, that a description of kidney targeting does not mean the particles exclusively localize in the kidneys nor does it mean that those particles are safe or effective in kidney disease therapy.

Generally, the NP systems that we found can be broken down among the broader classes of NPs (Figure 1 and Table 1): (*1*) lipid NPs or liposomes, (*2*) polymer NPs, (*3*) protein or nucleic acid NPs, and (*4*) inorganic NPs. This follows broad trends in the nanotechnology field and gives some insight as to the diversity of approaches currently being studied in the "kidney nanomedicine revolution."

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Table 1. Nanoparticle systems which have shown some kidney localization or been used to treat kidney disease

Nanomaterial	Tissue Within the Kidney	Kidney Localization Mechanism	Context or Demonstration
Lipid NPs/liposomes			
Liposome loaded with prednisolone[50]	Glomerular mesangium	Cationic lipid shows selective affinity to the anionic cell surface and ECM in glomerular mesangial lesions	Decreased deposition of IgA and C3 in glomeruli of ddY mice
Phospholipid NPs with surface peptides and celastrol loading[51]	Glomerular podocytes	Size, charge, and peptide modification mediated delivery shows affinity to VCAM1	Improved drug delivery to glomeruli, reduced toxicity of celastrol, reduced glomerular injury, and alleviated CKD in a mouse model through anti-inflammatory effect of the drug selectively delivered to endothelial cells and podocytes
Liposomes loaded with triptolide[52]	Glomerular mesangium	Cationic lipid TRX-20 shows high affinity to mesangial cells	Triptolide-mediated immunosuppression, anti-inflammatory effects in membranous nephropathy rat model
Liposomes coated with octa-arginine and loaded with siRNA against MAPK and p65[53]	Glomerular mesangium	Size-based (110 nm) penetration through glomerular endothelium pores and retention in the glomerulus due to cationic charge and size larger than podocytes foot processes	Reduced proteinuria, inflammation and ECM deposition in mouse model
DSPE-PEG2000-folate and DSPE-PEG2000-methoxy amphiphile NPs[54]	Tubular epithelium	Size-specific and folate-mediated passage through glomerulus	Kidney accumulation in healthy mice
Micelles with ([KKEEE]3K) kidney targeting peptide[55] (same group as the above entry)	Tubular epithelium	([KKEEE]3K) binds to megalin leading to receptor-mediated endocytosis	Kidney accumulation in healthy mice
Stearamine NPs loaded with enzymatic permanganate NPs[56]	Tubular epithelium	Inflammation-mediated enhanced kidney accumulation	Anti-inflammatory and antiapoptotic effects in the kidneys of IRI-AKI mice
Polymeric NPs			
PLL-PEG complexed with siRNA against MAPK1[57]	Glomerular mesangium	Penetration through glomerular endothelium fenestrae due to 10–20 nm size	Reduced proteinuria and protein expression in mouse model of GN
CDP-based siRNA NPs[58]	GBM	Binding and disassembly by components of the renal filtration barrier influenced by NP size (10–100 nm), positive zeta potential, and electrostatically driven self-assembly	GBM accumulation in healthy mice
Chitosan NPs with metformin[59]	Tubular epithelium	Megalin-mediated endocytosis	Antiapoptotic, anti-inflammatory, and antifibrotic effect in ureteralUUO mice
Chitosan/siRNA NPs targeting AQP1[60]	Tubular epithelium	Megalin-mediated endocytosis	AQP1 gene silencing in healthy mice
Chitosan/siRNA NPs targeting COX-2[61]	Renal macrophages	Phagocytic uptake by macrophages	Prevention of unilateral ureteral obstruction-induced kidney damage
PEG-PLGA NPs loaded with dexamethasone acetate[62]	Glomerular mesangium	Penetration through glomerular endothelium fenestrae due to 90 nm diameter	Glomerular mesangium targeting in healthy rats
Polymeric nanosponges based on a phosphoester that scavenges ROS[63]	Tubular epithelium	Increased microvascular permeability in AKI kidneys	Treatment of AKI by downregulation of ROS, inflammation, and reduction of cell apoptosis in a mouse model
Amphiphilic PAMAM polymer loaded with rosmarinic acid[64]	Tubular epithelium	Serine binding to KIM-1 and charge-mediated passage through GFB	Protection of cells from oxidative stress, decreased inflammatory response for therapy of AKI in a mouse model
PEG-PCL-PEI copolymer loaded with rhein[65]	Glomerular mesangium	Size-based penetration through glomerular endothelial membrane due to increased pore size in kidney disease	Kidney targeting, improvement of fibrinogen levels, and kidney function markers in diabetic nephropathy mouse model
Copolymer loaded with curcumin[66]	Tubular epithelium	Size, charge-based penetration through GFB	Alleviate mitochondrial injury, protect cells, and kidneys from oxidative stress in cisplatin-induced AKI mouse model
PVP loaded with curcumin[67]	Tubular epithelium	Size below renal excretion threshold (<10 nm)	Lessened kidney damage and restored kidney function in cisplatin-induced AKI mouse model

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Table 1. (Continued)

Nanomaterial	Tissue Within the Kidney	Kidney Localization Mechanism	Context or Demonstration
Hyaluronic acid conjugated to bilirubin loaded with a calcium chelator[68]	Tubular epithelium	CD44 binding capacity of Hyaluronic acid	Inhibition of activation of endoplasmic reticulum stress cascade, regulation of apoptosis pathway, reduced inflammatory response in AKI rat model
PEGylated gambogic acid NPs[69]	Tubular epithelium	Passage through GFB and enhanced retention in injured kidneys (<10 nm)	Protection of cells from oxidative stress damage, improving renal damage by antiapoptotic and anti-inflammatory activity in cisplatin- and rhabdomyolysis-induced AKI mouse models
Polyplex with siRNA against PCX[70]	Tubular epithelium	CXCR4-mediated transport to tubules	p53 gene silencing, improving kidney function and reduction in kidney damage therefore reducing AKI in cisplatin-induced and IRI-AKI mouse models
Modified chitosan NPs loaded with siRNA against p53[71] (same group as the above entry)	Tubular epithelium	Preferential internalization by injured tubule cells through CXCR4-mediated uptake	Decreased kidney apoptosis, macrophage and neutrophil infiltration, improved kidney function in IRI-AKI mouse model
PAMAM dendrimer modified with serine[72]	Tubular epithelium	Size-based glomerular filtration and active transport (<10 nm)	Kidney targeting in healthy mice
Copolymer of sorbitol and PEI loaded with plasmid DNA[73]	Tubular epithelium	Size-based endocytosis and targeting to vimentin	Alport syndrome mouse model showed enhanced transfection efficiency and uptake by cells
Pluronic NPs modified with folate loaded with triptolide[74]	Tubular epithelium	Folate receptor-mediated endocytosis	Reduced acute tubular injury index and renal function indexes in IRI-AKI mouse model
Polyplex with albumin loaded with celastrol[75]	Tubular epithelium	Megalin receptor-mediated internalization	Improved kidney function markers and renal injury in IRI-AKI mouse model
PLGA NPs loaded with oltipraz[76]	Tubular epithelium	PLGA NPs with 100 nm diameter cross through impaired GFB	Reduced tubular necrosis and collagen deposition, improved renal function and renal fibrosis in AKI mice model
Protein, peptide, and nucleic acid NPs			
Celastrol-albumin NPs[77]	Glomerular mesangium	Size-based (95 nm) penetration through glomerular endothelium leading to accumulation in mesangial cells	Alleviation of proteinuria, inflammation, and ECM deposition in rat GN model
Albumin NP loaded with farnesyl thiosalicylic acid[78]	Glomerular mesangium	Size-based (100 nm) penetration through glomerular endothelium and accumulation in mesangial space	Alleviation of renal fibrosis in UUO-induced renal fibrosis mouse model
DNA origami nanostructures[79]	Tubular epithelium	Glomerular endothelial fenestrae filtration influenced by morphology and size	Amelioration of rhabdomyolysis-induced AKI in mice by ROS scavenging
Small-sized DNA tetrahedrons with p53 siRNA[80]	Tubular epithelium	Size-based filtration through GBM and endocytosis into tubular cells (<10 nm)	siRNA-induced gene downregulation in AKI mouse model
Tetrahedral nucleic acid nanostructure loaded with typhaneoside[81]	Tubular epithelium	Size near renal excretion threshold and enhanced retention in AKI	Increased apoptotic and antioxidative function with kidney function restoration in IRI-AKI mouse model
Crotamine (cell-penetrating peptide)/siRNA nanocomplexes[82]	Tubular epithelium	Syndecan-1–mediated internalization in the brush border zone of PTECs	Accumulation in PTECs of healthy mice after IP administration
L-serine-modified Poly-L-Lysine with radiotracer[83]	Tubular epithelium	Size-based filtration in the glomerulus and absorption in the lumen of proximal tubule	Reduced renal tumor growth and nephrotoxicity in a mouse model
Protein-based nanocage[84]	Tubular epithelium	Size-based filtration through glomerular endothelium and reabsorption by proximal tubules	Mitigation of proximal tubular damage in a mouse model of sepsis-induced kidney injury
Inorganic NPs			
Perfluorocarbon NP with collagen IV loaded with prednisone[85]	GBM	Col4-targeting ligand selectively binds to collagen IV on GBM	Decreased IgG and C3 deposition, reduced proteinuria, improved GFR presentation, reduced glomerular pathology in lupus nephritis mouse model
Quantum dots that chelate iron[86]	Tubular epithelium	Size-based penetration through glomerular endothelial membrane (<10 nm)	Decreased ferroptosis and apoptosis, removal of iron species and ROS in cisplatin-induced AKI mouse model

Table 1. (Continued)

Nanomaterial	Tissue Within the Kidney	Kidney Localization Mechanism	Context or Demonstration
Selenium NPs with albumin[87]	Tubular epithelium	Endocytosis by RTEC	Suppression of inflammasome and cytokines in IRI-AKI mouse model
Iron oxide NPs loaded with nicotinamide[88]	Tubular epithelium	Size-based penetration through glomerular endothelial membrane and NRK1-mediated cellular uptake	Repair of renal structure, restoration of eGFR and hemoglobin elevation in AKI mouse model
Gold NPs[89]	Tubular epithelium	Size-based penetration through GFB (<10 nm)	Reduction of ROS and apoptosis in a mouse model of subclinical AKI
Gold NPs with PEG[90]	Glomerular mesangium	Size-based targeting (approximately 75±25 nm)	Mesangium targeting in healthy mice
Hydrogenated germanene nanosheet[91]	Tubular epithelium	DNA-like framework and negative surface charge and PEG modification-based accumulation	Antioxidative protection against ROS in AKI mouse model
Carbon nanotubes with siRNA conjugated against p53, Mep1b, Ctr1, and EGFP[92]	Tubular epithelium	Glomerular filtration and reabsorption at proximal tubular cell brush border	Prevention of cisplatin-induced AKI in murine model
Mesoporous silica NP loaded with BAPTA[93]	Tubular epithelium	Size-based penetration through glomerular membrane and active targeting with KIM-1 targeted peptide	Antiapoptotic and anti-inflammatory effect restoring kidney function in a rat IRI-AKI model
Zeolite imidazolate NPs coated with tubular epithelial cell membrane[94]	Tubular epithelium	Active targeting through RTEC membrane coating and modification with kidney targeting peptide	Attenuation of oxidative and inflammatory damage and recovery of renal function in sepsis-induced AKI murine model

"Kidney localization mechanism" does not necessarily signify that the kidney is the only, or primary, site of tissue accumulation in the body. AQP1, aquaporin 1; BAPTA, O,O′-bis(2-aminophenyl)ethyleneglycol-N,N,N′,N′-tetraacetic acid; CD44, cluster of differentiation 44, a cell surface glycoprotein; CDP, cyclodextrin-containing polymer; CLT, celastrol, an active ingredient with anti-inflammatory, antioxidant, immunosuppressive, and antitumor effects[56]; COX-2, cyclooxygenase type 2; Ctr1, copper transport protein 1; CXCR4, C-X-C chemokine receptor 4; DSPE-PEG2000, 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-*N*-[amino(polyethylene glycol)-2000]; ECM, extracellular matrix; EGFP, enhanced green fluorescent protein; ER, endoplasmic reticulum; FBG, fasting blood glucose; GBM, glomerular basement membrane; GFB, glomerular filtration barrier; IV, intravenous; IRI, ischemia–reperfusion-induced; KIM-1, kidney injury molecule-1; MAPK, mitogen-activated protein kinase; Mep1b, meprin-1β; NP, nanoparticle; NRK1, nicotinamide riboside kinase 1; Oltipraz, a drug for treatment of AKI and renal fibrosis[81]; PAMAM, polyamidoamine; PCX, polymeric CXCR4 antagonist; PEG-PCL-PEI, polyethyleneglycol-co-polycaprolactone-co-polyethylenimine; PEG-PLGA, polyethylene glycol-poly(lactic-coglycolic acid); PEI, polyethylenimine; PLGA, poly(lactic-co-glycolic acid); PLL-PEG, poly(l-lysine)-poly(ethylene glycol); PTEC, proximal tubular epithelial cells; PVP, polyvinylpyrrolidone; RTEC, renal tubular epithelial cell; ROS, reactive oxygen species; siRNA, short interfering RNA; TP, triptolide, a drug with immunosuppressive properties[57]; TRX-20, 3,5-dipentadecyloxybenzamidine hydrochloride; UUO, unilateral uretral obstruction; VCAM1, vascular cell adhesion molecule 1ureteral.

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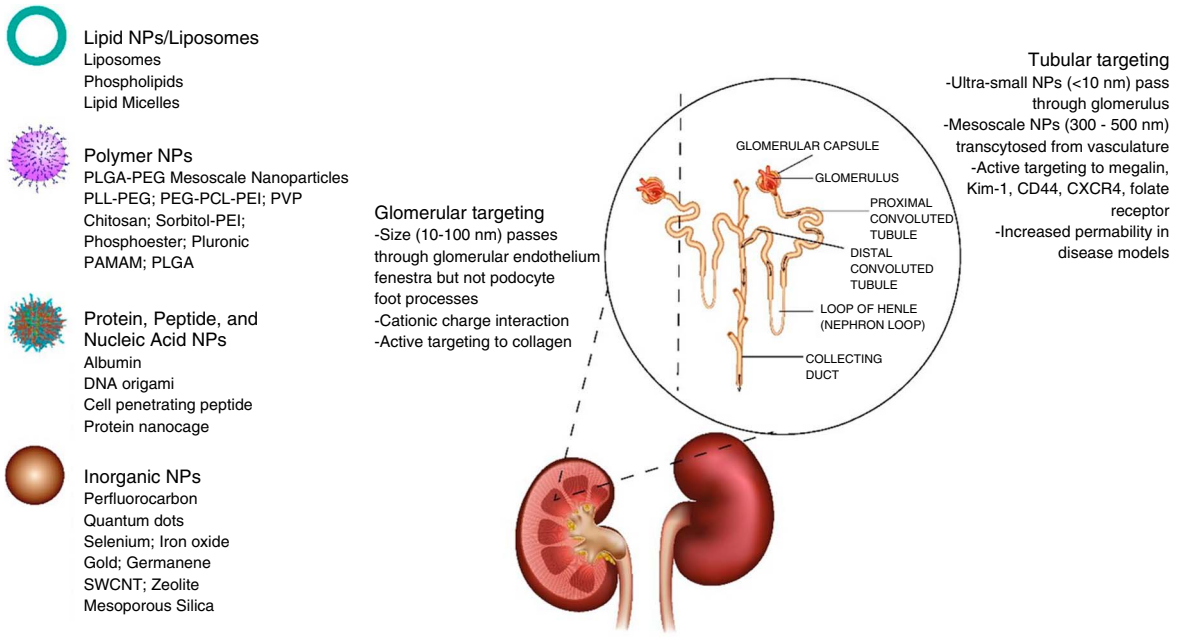

Figure 1. NP systems and their uses in kidney diseases. Examples of major classes of NPs used in kidney-specific targeting are shown on the left. On the right, the nephron is shown with examples of strategies that have been used to target the glomerulus and tubules. CD44, cluster of differentiation 44, a cell surface glycoprotein; CXCR4, chemokine receptor type 4, a stromal-derived factor 1 receptor; NP, nanoparticle; PAMAM, polyamidoamine, a hyperbranched polymer dendrimer; PCL-PEI, polycaprolactone-polyethylene imine, an amphiphilic block copolymer; PLGA-PEG, poly (lactic-*co*-glycolic acid)-polyethylene glycol, an amphiphilic block copolymer; PVP, polyvinylpyrrolidone, a hydrophilic polymer; SWCNT, single-walled carbon nanotube, a nanoscale carbon tubule.

Several of these systems have been tracked by the investigators over several publications, including particles which pass through glomerular fenestrations allowing component breakdown and tubular delivery,[58,90,95] size-based carbon nanotube penetration through the glomerulus and reabsorption by proximal tubules which has been studied in mice and nonhuman primates,[92,96] and lipid micellar particles with active targeting agents.[47,54,55]

The kidney-targeting mechanisms, or mechanisms for enhanced renal accumulation, fall into two broad categories (Figure 1): (*1*) passive targeting through largely size-based accumulation and (*2*) active targeting, wherein a specific molecule that binds to renal cells was used. Several passive targeting approaches were used, including: (*1*) small NPs (<10 nm) which pass through the glomerular filtration barrier and are reabsorbed in the nephron, (*2*) somewhat larger NPs which pass through the glomerular endothelial fenestrations and arrest in the glomerular mesangium (typically up to 80 nm), (*3*) somewhat larger (approximately 100 nm) NPs which pass through only disrupted glomerular filtration barriers and are reabsorbed in the nephron, and (*4*) NPs which do not interact with the glomerulus and cross from the peritubular endothelium into the tubular epithelium. Active targeting of NPs to the kidneys has taken several different approaches, including serine modifications which purportedly bind kidney injury molecule-1,[64,71,83,93] charge-based binding to the megalin receptor,[55,59,60,75] or other cell surface receptor or basement membrane binding.[51,68,70,85]

Regarding therapeutic cargoes, we found that many of the active pharmaceutical ingredients (APIs) involved short interfering RNA (siRNA) delivery—about 10 of those we found. Many others incorporated natural products, often with reactive oxygen species scavenging capabilities, or the material itself acting as a reactive oxygen species scavenger.[63,79] The disease models which were investigated have similarly been wide-ranging. AKI mouse models of several etiologies have been investigated, as well as fibrotic CKD and glomerular nephropathies. A few, but not many, studies investigated therapeutic efficacy in renal carcinoma models, while some performed biodistribution studies in healthy animals. In most cases, positive therapeutic efficacy was reported as it relates to one or several renal function outcomes, and no toxicity was found if reported.

Polymeric Mesoscale NPs—Tubular Kidney Targeting at the Meso-Nanoscale

As we outlined above, there are a variety of NP systems that either target the kidneys with some selectivity or demonstrate therapeutic efficacy in kidney disease models or both. The compilation of these systems and their potential use has been described in an array of recent review articles, which we overviewed above. One such system, polymeric mesoscale NPs (MNPs), has demonstrated both the most substantial renal selectivity, as well as the most flexibility in therapeutic payload and disease indication (Figure 2). To date, there have been 13 publications based on this delivery platform, with several directly from our group, some with collaborators, and some from other groups independently. Generally, if the authors ascribed their kidney targeting mechanism to the particles being in

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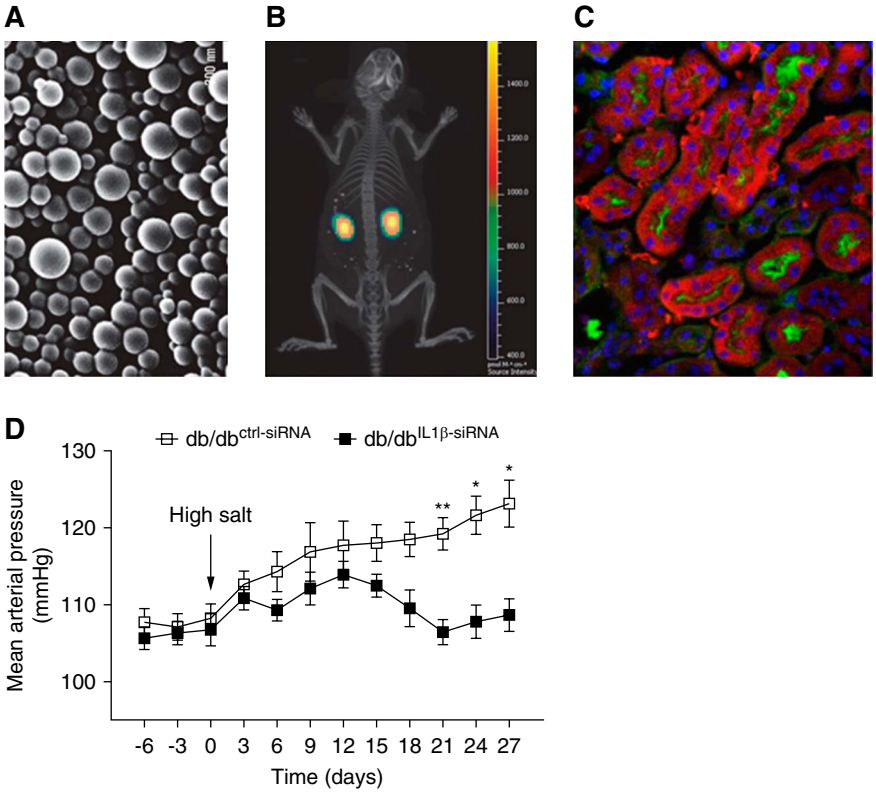

Figure 2. MNPs target the proximal tubular epithelium and are therapeutically effective in kidney disease. (A) Scanning electron micrograph of MNPs. (B) IVIS fluorescence image focused on the kidneys overlain on a CT of a mouse injected with fluorescent dye-loaded MNPs (reprinted with permission from Williams *et al.*[97] Copyright 2015 American Chemical Society). (C) Fluorescence micrograph of renal tissue after injection of MNPs. Blue is nuclei, green is proximal tubular epithelial lumen, and red is anti-PEG staining for MNPs. (reprinted from Han 2020 *Kidney International* with permission from Elsevier[98]). (D) BP of db/db mice treated with control siRNA-loaded MNPs or IL-1β siRNA-loaded MNPs. (reprinted with permission from Veiras *et al.* 2022 *Circulation Research* with permission from Elsevier[99]). CT, computed tomography; MNP, mesoscale nanoparticle; siRNA, short interfering RNA.

the mesoscale range, we considered those here as opposed to above.

In our prior work, we published that polymeric NPs in the so-called "mesoscale" range, approximately 300–500 nm in diameter, demonstrated substantial kidney targeting.[97,101] These particles were initially formulated *via* nanoprecipitation using FDA-approved di-block polymers poly(lactic-*co*-glycolic acid) conjugated to polyethylene glycol. The first two publications on MNPs were focused on understanding their pharmacology, primarily using a hydrophobic Cy5 (cyanine) fluorescent dye cargo. Experiments investigated routes and concentrations of administration, with almost all studies using an intravenous dose of 10–100 mg/kg MNP. Using *in vivo* and *ex vivo* imaging coupled with immunohistochemistry, published studies determined that MNPs localize to the kidneys 26-fold greater than any other organ investigated.[97,101,102] Proximal tubular epithelial cells were the primary tissue of localization, with some distal tubular localization (approximately 2:1 proximal:distal) and no glomerular uptake. Those studies concluded that MNPs were not filtered by the glomerulus, but instead transcytosed across the peritubular epithelium into the basolateral membrane of tubular epithelial cells. Furthermore, these experiments found no evidence of toxicity either systemically or localized in the kidneys. Generally, these particles and their cargoes have demonstrated long renal retention times, up to several days or weeks, with controlled release and extended pharmacodynamic profiles. Given this safety and kidney targeting profile, MNPs were further used as carriers for therapeutic cargoes in kidney diseases.

Diversity of MNP Cargoes: Small Molecules, Peptides, and Nucleic Acids/siRNA

Polymeric MNPs which target the kidneys with high selectivity have been demonstrated to encapsulate and deliver a broad range of various cargoes (Table 2). Modifications from those original dye-loaded MNP formulations were required to ensure that the size (300–500 nm diameter in all studies) and overall surface chemistry (PEGylated) were similar to ensure kidney targeting.

Several small molecule cargoes have been successfully encapsulated and delivered to the kidneys *via* MNPs. Encapsulation of small molecules is relatively straightforward in the nanoprecipitation process for drugs, with minor modifications to account for drug solubility. This includes hydrophobic small molecules, such as Cy5 and Cy7 dyes, that have been used for imaging and biodistribution

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Table 2. Pharmacologic and therapeutic studies using polymeric mesoscale nanoparticles

MNP Payload	Disease Target/Use	Therapeutic Outcomes (Compared with Baseline Control)	Pharmacokinetics	Notes
Fluorescent Cy5 dye[97]	Healthy mice/pharmacology	N/A	Seven-fold kidney targeting, tubular specific by IHC (PEG)	Initial discovery and characterization, compared with free dye
Fluorescent Cy5 dye[101]	Healthy mice/pharmacology	N/A	26-fold kidney targeting by IV and dose modulation, PTEC specific, no toxic effects in liver, serum, kidneys	Dose and route modulation, pharmacology study, compared with free dye
ODN2088 selective TLR9 antagonist, nucleic acid[98]	Ischemic AKI	60%–90% reduction in creatinine, BUN, H&E injury, NGAL, infiltration of macrophages and neutrophils, apoptosis, cytokine signaling	30-fold kidney targeting (Cy5 dye) in healthy and IR mice, PTEC specific by IF (PEG)	Compared with free drug control with positive benefits
Triptolide small molecule, Cy7 dye[102]	Ischemic AKI	80%–100% reduction in H&E injury, creatinine, BUN, C3, apoptosis	Eight-fold kidney targeting (drug LC-MS and Cy7 fluorescence); no toxic effects in liver or other organs, protective effect from drug toxicity	First replication by external groups, compared with free drug with benefits
NEMO binding peptide[103]	Ischemic AKI	40%–60% reduction in creatinine, BUN, H&E injury, NGAL, apoptosis, neutrophil infiltration, cytokine signaling	PTEC specific by IHC (PEG) with no staining in other organs	Similar results compared with NEMO-deleted mice
Emodin small molecule, Cy7 dye[104]	UUO CKD	Reversal of fibrosis by H&E (not quantified)	Primarily kidney targeting (not quantified), no in vitro toxicity	
Sirolimus small molecule[105]	ADPKD rats (*Pkhd1*$^{PCK/PCK}$)	75%–95% reduction in renal cyst volume, pS6/S6 ratio	Increased body and heart weight compared with free sirolimus, indicated less toxicity compared with free drug	Published conference proceedings, stronger performance than free drug
Formoterol small molecule[106,107]	Healthy mice/pharmacology	Increase in mitochondrial biogenesis in the renal cortex, none in the heart	Proximal tubular localization by IF (PEG), 15-fold enhancement of drug targeting compared with free drug	
Formoterol small molecule, Cy5 dye[108]	Ischemic AKI	80%–100% reduction in creatinine, KIM-1, NGAL, fibrosis, increase in mitochondrial production	No effects on heart rate or BP (free drug showed effects)	Size 463–493 nm. Compared effects with free drug control at higher dose with benefits
Edaravone small molecule[100,109]	Cisplatin-induced AKI	70%–100% reduction in creatinine and BUN, NGAL, oxidative stress by IHC (nitrotyrosine)	PTEC-specific targeting by IHC (PEG), renal accumulation compared with none with free drug	Preprint demonstrates kidney targeting in flank xenograft and lung tumor-bearing mice
Renalase agonist peptide RP81[110]	Cisplatin-induced CKD in renalase knockout and WT mice	70% reduction in creatinine, KIM-1, inflammation, cell death	PTEC-specific targeting by IHC (RP81)	
siRNA against PDL1[111]	Hypertensive CKD in mouse DOCA+salt model	100% reduction in PDL1 expression, reduction in CD8 T cells, baseline BP	No effects on BP of MNPs alone, no MNP-induced T cell infiltration, no siRNA-induced KD in lung, liver, or spleen	Showed results similar to IFNγ knockout mice, single dose showed KD 18 d later
siRNA against IL-1β[99]	Diabetic kidney disease (db/db mice)	75%–100% reduction in IL-1β expression compared with baseline, baseline BP, and inflammation, salt sensitivity	No effects on body weight, glucose, insulin; no siRNA-induced KD in plasma, heart, aorta, iver, spleen; no effects on BP alone	Showed results similar to knockout of IL-1 receptor, MNPs dosed twice/every other week
siRNA against OCT 1 and 2, p53, PKCδ, γGT[112]	Cisplatin-induced AKI	50%–80% reduction in creatinine, BUN, fibrosis (PAS), target KD	No cell toxicity	MNPs were chitosan with PEG coating

ADPKD, autosomal dominant polycystic kidney disease; DOCA, deoxycorticosteroid acetate; γGT, γ-glutamyl transpeptidase; H&E, hematoxylin and eosin stain; IF, immunofluorescence; IHC, immunohistochemistry; IR, ischemia–reperfusion; IV, intravenous; KD, knockdown; KIM-1, kidney injury molecule-1; LC-MS, liquid chromatography-mass spectrometry; MNP, mesoscale nanoparticle; NEMO, nuclear factor-κB essential modulator; N/A, not applicable; NGAL, neutrophil gelatinaseassociated lipocalin; OCT, organic cation transporter; PAS, periodic acid–Schiff staining; PDL1, programmed death-ligand 1; PKCδ, protein kinase C delta; PTEC, proximal tubular epithelial cell; siRNA, short interfering RNA; TLR9, toll-like receptor 9; UUO, unilateral uretral obstruction; WT, wild type.

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studies.[97,101,102,104,108] It also includes hydrophobic APIs formoterol,[106–108] triptolide,[102] emodin,[104] and rapamycin,[105] as well as slightly hydrophilic edaravone.[100] These small molecules cover several mechanisms of action: β_2-adrenergic receptor agonist formoterol; anti-inflammatory natural products triptolide and emodin; redox scavenging for edaravone; and mammalian target of rapamycin inhibitor rapamycin. It is important to note that several of the above APIs were directly compared with free drug without MNP delivery or indirectly compared with prior studies. In each case, MNP-enabled delivery to the kidneys demonstrated a favorable therapeutic and safety profile compared with the free drug alone.

Biologically active nucleic acid cargoes have also been demonstrated to be therapeutically efficacious in kidney diseases following MNP-encapsulated delivery. Slight modifications in formulation are typically necessary for such large hydrophilic APIs, usually incorporating a solvent-aqueous phase mixture before nanoprecipitation. The first such example was an oligodinucleotide toll-like receptor 9 antagonist ODN2088.[98] There have since been three different publications demonstrating therapeutic siRNA-loaded MNP formulation and kidney delivery: siRNA targeting the inflammatory cytokine IL-1β,[100] the CD8 T-cell regulating programmed death-ligand 1,[111] and simultaneous delivery of an siRNA cocktail against organic cation transporters—1 and 2, p53, protein kinase δ, and γ-glutamyl transpeptidase.[112] It is exciting that, in all cases, kidney-specific knockdown of the siRNA target was demonstrated, in one case up to 3 weeks after a single dose, with no knockdown in other organs observed.[111] In addition, loading of mRNA into MNPs and expression of a reporter protein (mCherry) in renal tubular cells in vitro has been reported.[113] The ability to load and deliver functional nucleic acids to the kidneys, and generally anywhere beyond the liver, is an extremely important and exciting development in gene delivery science. The plug-and-play nature of siRNA and mRNA, coupled with recent developments in those fields, potentiates many therapeutic applications across a broad range of kidney diseases.

An additional category of demonstrated MNP-loaded APIs is peptides and proteins. There have been two manuscripts published using these cargoes: a peptide binding to nuclear factor-κB essential modulator[103] and a peptide agonist of renalase.[110] In both cases, MNP-targeted peptide delivery demonstrated superior efficacy to free peptide, although ongoing work is necessary to validate full-protein delivery.

Therapeutic Efficacy in Kidney Disease Models: AKI and CKD of Various Etiologies

While there have been several types of cargoes loaded into MNPs, they have similarly been applied to kidney disease models of several etiologies. Both acute and chronic models have been investigated, with a variety of dosing strategies, including single-dose and multidose regimens. Furthermore, basic pharmacology has been studied in both healthy and diseased rodents, with original discovery and validation of MNPs occurring in hairless immunocompetent and wild type mouse strains.[97,101,106,107] Interestingly, kidney-specific targeting has been demonstrated in nude and nod-scid gamma mice bearing flank and orthotopic lung tumors in work designed to avoid NP localization to tumors in chemotherapy-associated AKI.[109] It should be noted that most studies have been performed in mice to date, with one initial work in rats.

AKI models have been the most widely investigated for MNP application. The most common AKI etiology has been the ischemia–reperfusion model, with therapeutic effects stemming from a toll-like receptor 9 antagonist oligodinucleotide, nuclear factor-κB essential modulator binding peptide, formoterol, and the small molecule triptolide.[98,102,103,108] Cisplatin-induced models of AKI are also commonly used in the field, with successful demonstration of both an siRNA cocktail and small molecule edaravone delivery.[100,112] Although the siRNA cocktail delivery and triptolide delivery studies were administered daily for 3 days, the other AKI studies described here were single administrations associated with model initiation or up to 24 hours after.

MNP-targeted delivery and efficacy has also been demonstrated in CKD models. These included the unilateral ureteral obstruction model,[104] a chronic cisplatin-induced model,[110] hypertensive deoxycorticosteroid acetate+salt mice,[111] and hypertensive diabetic (db/db) mice (Figure 2D).[100] Notably, initial studies in a polycystic kidney disease model have also been published as a proffered abstract using an autosomal recessive polycystic kidney disease rat model, administering rapamycin-MNPs twice weekly for 8 weeks. In these models, only the programmed death-ligand 1–targeted siRNA-MNPs were administered just once (deoxycorticosteroid acetate+salt), while the anti-IL-1β siRNA-MNPs were administered every other week for 6 weeks (db/db mice), emodin-MNPs were administered daily (unilateral uretral obstruction), and renalase peptide MNPs were dosed weekly for 4 weeks (cisplatin CKD).

Conclusions and Call to Action

Here, we described the state of the art regarding several highly promising NP systems for kidney-targeted drug delivery, with a specific focus on one system that has demonstrated the broadest utility to date, albeit for tubule-specific targeting. Many of the studies have considerably strong results in preclinical rodent models of disease. Notably, several of these studies extended beyond basic formulation and demonstration of the materials, instead focusing on using kidney-targeted NPs as chemical biology tools to better understand underlying disease processes through targeted pathway inhibition.[114] However, substantial work remains to translate these toward clinical utility. Proceeding to investigational new drug applications and clinical trials will be disease-specific and investigator-driven, meaning decisions on which cargoes to use and pathways to target must be made rationally based on substantial preclinical evidence. This will include full preclinical pharmacology and toxicology studies in both rodents and larger mammals, such as pigs or nonhuman primates. Design and carry forward of such a potential agent will require buy-in and collaboration of industry, clinicians, the venture community, and others. We are confident, however, that given the recent clinical successes of nanomedicines, that this class of therapies will soon make an effect on the kidney disease community.

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Disclosures

R.M. Williams reports the following: Consultancy: Goldilocks Therapeutics, Inc.; Ownership Interest: Goldilocks Therapeutics, Inc.; Patents or Royalties: Patents pending regarding kidney targeting NP formulation, no royalties received. Advisory or Leadership Role: Goldilocks Therapeutics, Inc. advisory role; and Other Interests or Relationships: Goldilocks Therapeutics, Inc. All remaining authors have nothing to disclose.

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