Nanomedicines for kidney diseases

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Nanomedicines have been the subject of great interest for the treatment, diagnosis, and research of disease; however, few specifically address kidney disorders. Nanotechnology can confer significant benefits to medicine, such as the targeted delivery of drugs to specific tissues. Nanomedicines in the clinic have increased drug solubility, reduced off-target side effects, and provided novel diagnostic tools. There is an increasing cohort of nanomaterials that may have implications for kidney disease. Here, we review nanomaterial properties that are potentially applicable to kidney research and therapy, and we highlight clinical areas of need that may benefit from kidney nanomedicines.

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Nanomaterials can loosely be defined as engineered macromolecules in the size range of 1 to 1000 nm.[1] The types of materials involved are broad and can include lipids, modified biomacromolecules, polymers, metals, semiconductors, and others. Many nanomaterials have unique physical properties conferred by their size.

Nanotechnology applications in medicine

Drug delivery. One of the most common uses of nanoparticles (NPs) is in the delivery and controlled release of therapeutic molecules. Nanomaterials have been engineered to incorporate small molecule drugs as well as macromolecules such as nucleic acids, proteins, and peptides. One advantage of encapsulating therapeutic drugs in NPs includes the suspension of otherwise insoluble drugs.[2] Perhaps the greatest promise of nanomedicines for drug delivery applications is the ability to control drug pharmacokinetics.[1] Many potentially therapeutic molecules exhibit poor pharmacokinetics, especially with respect to the kidneys. Many small molecule therapies are cleared from the body renally, but their persistence in the kidneys is too brief to achieve a therapeutic effect. Compounds that are cleared by hepatobiliary mechanisms may have even less exposure to the kidneys.

The targeting of NPs to specific organs, tissues, and cells in the body would allow for the reduction of off-target side effects of drugs that produce toxicities when administered conventionally. The physical targeting of drugs may also enable a reduction in the total administered dose, as more payload is available at the disease site instead of healthy organs.[3] Targeting is often achieved through the use of molecular recognition entities such as antibodies, peptides, nucleic acids, or small molecules, which may be attached to or coat NPs.[3]

Nanomaterials incorporating therapeutic molecules can be engineered to control the rate of drug release. Nanomedicines can be administered in a depot format, allowing timed-release and single-dose administrations to achieve an optimal therapeutic index.[4] Also, NPs may protect encapsulated molecules from degradation in the body.[3] This strategy can be combined with encapsulation or conjugation of therapeutic or imaging payloads to design a functional material.

Other therapeutic mechanisms. NPs can also have other desirable therapeutic properties. Among these is the potential for photothermal therapy, often in oncology applications. Nanomaterials composed of certain metals including gold and silver can produce an increase in local temperature because of light-induced plasmon resonance—a physical property that can only be exploited at nanoscale dimensions.[5] Such plasmonic nanomaterials are often targeted by molecular

recognition entities to specific tissues before exposure to light, producing a temperature elevation to kill the targeted cells. Another potential therapeutic use of nanomaterials is the selective sequestration and removal of toxic substances, often through the use of magnetic nanomaterials.[6]

Diagnostics. The intrinsic properties of certain nanomaterials, most often metallic, may facilitate applications in medical diagnostics. NPs are often considered as contrast agents for magnetic resonance imaging (MRI) and computed tomography because of intrinsic paramagnetic or electron-dense material properties, or the ability to encapsulate radiometals.[7–9] Such materials have the potential to prevent renal toxicity of conventional contrast agents. Other diagnostic functions of NPs can stem from properties specific to nanoscale materials, such as gold NPs developed to detect cancer facilitated by the signal enhancement afforded by plasmon resonance effects.[10] 'Theranostics' are technologies, often involving nanomaterials, with both diagnostic and therapeutic capabilities. Some examples pair the two capabilities, allowing the technology to monitor or control the administration of therapy.[11]

Research tools. An important application of nanotechnologies in the biomedical sciences is in the development of new research tools. Nanotechnologies are being developed to monitor analytes and processes in tissue culture and *in vivo*, including blood flow, renal filtration, and cardiovascular function.[12] Examples of a commercially available nanomaterial are quantum dots, which are semiconductor nanocrystals that emit bright fluorescence due to the quantum confinement effect.[13] The fluorescence output of quantum dots is relatively photostable and depends on tunable properties such as NP size and chemical composition, facilitating multicolor imaging capabilities.

Pharmacokinetics of NPs

The localization of nanomaterials to specific sites in the body can be modulated by changing particle size and surface chemistry, including the attachment of molecular recognition entities[14] (Figure 1). Depending on these factors, NPs can be targeted to specific parts of the nephron, may be filtered by the kidneys, or may avoid the kidneys entirely. Currently, the overwhelming majority of nanomaterials synthesized and intravenously administered to animals are known to accumulate in the liver and spleen.[14] NPs smaller than 200 nm in diameter can extravasate through fenestrations in the liver endothelium. In addition, NPs can be taken up by macrophages that migrate to the liver, lymph nodes, and spleen, or by macrophages resident to liver sinusoids (Kupffer cells).[15] Macrophage uptake is mediated in part by NP opsonization—the binding to serum proteins—which marks them for phagocytosis as part of the complement activation cascade.[15] This process can be avoided to some degree by reducing the

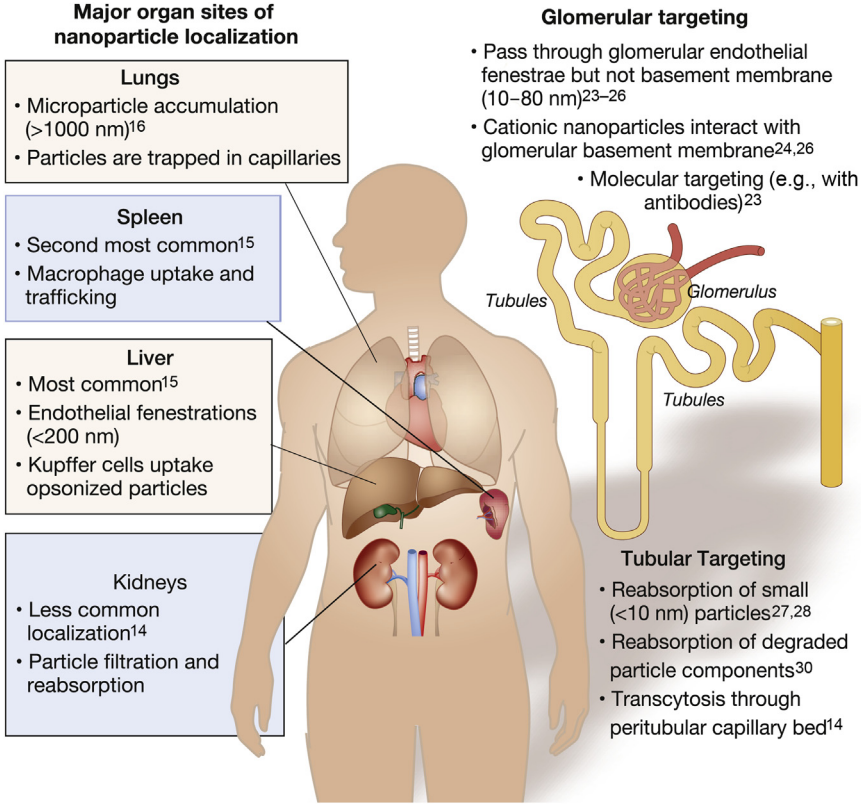

Figure 1 | Major sites of nanoparticle localization in the body and kidneys. Major sites of nanoparticle localization to different major organs in the body and hypothesized mechanisms of uptake (left). Strategies for targeting nanoparticles to renal tissues and hypothesized mechanisms of localization (right).

likelihood of opsonization of the NP by altering its surface chemistry. This is often done by attaching polyethylene glycol to the NP.[14,15] Microparticles, which are above the nanoscale size range (>1000 nm), can accumulate in the lungs by retention in alveolar capillaries.[16] Methods for targeting NPs to tissues and disease sites in the body other than the kidneys have been reviewed extensively elsewhere.[17,18] NP size, chemistry, and payload can be modified extensively to modulate their pharmacologic properties.[15,19]

Many nanomaterials exhibit renal clearance. This is a highly desirable pharmacokinetic property for elimination of potentially toxic metal nanomaterials, such as those used for diagnostic imaging.[20] To be cleared by renal filtration, NPs must be small enough to pass through the glomerular endothelial fenestrae (~100 nm) and the podocyte slit diaphragm (~8-nm pores).[20] Renal filtration may allow for the imaging of the kidney during the excretion process[21] and to study renal functions.[22]

NP targeting of renal tissues

There are no clinically approved NPs that specifically target the kidney for therapeutic or imaging applications. However, several recent preclinical studies describe nanomaterials that appear to selectively target renal tissues.

Glomerular targeting. Various studies describe the targeting of NPs to the glomerulus, portending the targeted treatment and imaging of this part of the kidney.[23] Within the glomerulus, NPs have been shown to target the glomerular basement membrane and mesangial cells.[24–26] One study describes the localization of polyethylene glycol–coated gold NPs 80 nm in diameter in mesangial cells, although the majority of the particles accumulated in the liver.[25] Follow-up work has suggested that similarly sized NPs transporting small interfering RNA (siRNA), composed of cationic polymers, can accumulate and disassemble in the glomerular basement membrane.[26] NP surface charge appears to affect glomerular deposition. Cationic ferritin NPs 13 nm in diameter accumulated in the rat glomerular basement membrane, while negatively charged ferritin NPs did not.[24] Additionally, investigators have conjugated specific targeting agents such as antibodies to nanomaterials to increase their glomerular localization (also reviewed in the article by Zuckerman and Davis[23]).

Tubular targeting. There have been few successful attempts to develop NPs that target the renal tubules. One described strategy is the engineering of NPs small enough to pass through the glomerular filtration barrier, which subsequently could be absorbed by epithelial cells lining the lumen of the nephron.[27,28] This strategy is similar to that used for low molecular-weight polymers and proteins.[29]

A second strategy has used biodegradable nanomaterials that pass through glomerular endothelial fenestrations but not the glomerular basement membrane.[30] The hypothesized mechanism of uptake was degradation of the NP at this deposition site and subsequent megalin-mediated uptake of the degradation products by the luminal membrane of proximal tubular epithelial cells.

The authors of this review recently found selective targeting of the proximal tubules by large "mesoscale" NPs that were much larger (~400 nm) than the fenestration of the glomerular basement membrane.[14] The authors hypothesized a mechanism whereby the NPs transcytosed across peritubular capillaries to be endocytosed by proximal tubule epithelial cells from the basal size of the tubule. These NPs localized in the kidneys with high specificity—up to 7 times greater than any other organ (Figure 2).

Nanomedicines in the clinic

Many nanotherapeutics have entered clinical trials, and several nanomedicines have achieved Food and Drug Administration approval for use in patients. Several nanomedicines are approved for use in oncology. The first Food and Drug Administration–approved therapeutic NP was Doxil in 1995, a PEGylated liposome-encapsulating doxorubicin designed to reduce cardiotoxicity.[31] Other chemotherapeutic-encapsulating nanoformulations that have progressed to the clinic include daunorubicin (DaunoXome), cytarabine (DepoCyt), and protein-bound paclitaxel (Abraxane).[32]

NP-based contrast agents have also been approved for use in the clinic. These include Technetium-99m sulfur colloid, a radiopharmaceutical used for sentinel lymph node mapping

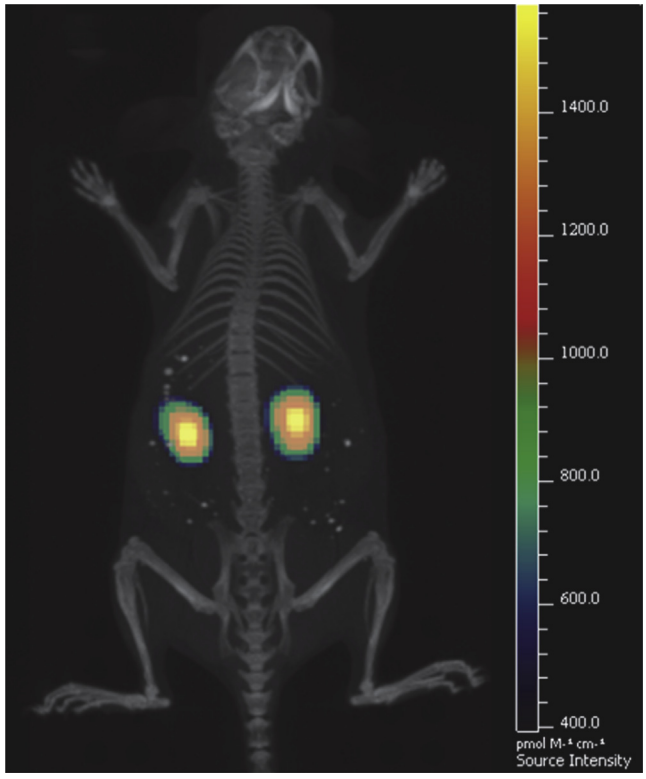

Figure 2| Fluorescence plus CT overlay focused on the kidneys of a mouse treated with mesoscale nanoparticles showing localization and relatively homogenous distribution throughout the kidneys. Reprinted with permission from Williams RM, Shah J, Ng BD, et al. Mesoscale nanoparticles selectively target the renal proximal tubule epithelium. *Nano Lett*. 2015;15:2358–2364. Copyright 2015 American Chemical Society.[14]

in breast cancer,[33] and ferumoxides (Feridex), a superparamagnetic iron oxide NP for MRI of lymph node and liver metastases.[34] A review listing nanomaterials in clinical trials or already Food and Drug Administration approved has been published recently.[32]

Applications in the treatment of kidney disease

Given recent technological developments of nanomaterials and new capabilities for interactions with the kidneys, great potential lies in their application for the treatment, diagnosis, and research of kidney diseases (Table 1). We describe potential disease applications below and note recent examples of kidney nanomedicine investigations.

Imaging and diagnostics in renal disease. NP-based MRI has been used as a strategy to detect early changes that could be consistent with acute kidney injury (AKI). Dendrimer-based nanomaterials for MRI have been shown to detect changes consistent with AKI before a rise in creatinine in mouse models.[35] A dendrimer is a repetitively branched polymer that takes the form of a sphere. In rat models of renal injury, ultra-small superparamagnetic iron oxide NPs have been used for MRI imaging, allowing the distinction between renal intrinsic disease and obstructive uropathy, as well as to identify the signs of kidney rejection.[36] Silica NPs with fluorescent anti-CD11 also have been used as an imaging tool for inflammation and fibrosis in animal models of obstructive uropathy.[37]

Hypertension. Several NP formulations have been used experimentally for the treatment of hypertension as a strategy to overcome problems associated with delivery and bioavailability of specific agents. The free-radical scavenger coenzyme Q10 has shown some potential in the treatment of hypertension by inducing vascular relaxation.[38] Poly(lactic-co-glycolic acid)–formulated NPs containing coenzyme Q10 were found to have greater oral bioavailability and to effectively reduce blood pressure in an animal model of hypertension.[39]

Nano-suspensions containing 1,3-Dicyclohexyl urea, a potent inhibitor of the degradation of the vasodilatory eicosanoid epoxyeicosatrienoic acid, were shown to be orally bioavailable and effective in reducing blood pressure in animal models of hypertension.[40] NPs loaded with siRNA against angiotensinogen were also shown to effectively reduce blood pressure in rat models of hypertension,[41,42] and nano-formulated superoxide dismutase has been shown to attenuate angiotensin II-induced hypertension.[43] In addition, nanomedicines have been used to increase the bioavailability of drugs already in use for hypertension, including nebivolol, candesartan, felodipine, olmesartan, and ramipril.[44–48]

AKI. AKI is a complex disease in which a variety of mediators play an important role, including nitric oxide (NO), reactive oxygen species, proinflammatory and profibrotic cytokines, among others.[49] Given the paucity of effective therapies for AKI, the use of NP-based approaches to deliver molecules specifically to the kidney to treat AKI is attractive and it is starting to be explored in animal models. Cerium oxide NPs that scavenge reactive oxygen species reduced AKI severity in a rat model of peritonitis-induced AKI.[50] Treatment with a thrombin-inhibiting NP was shown to improve renal function in mice when administered after induction of AKI.[51] Further, antiapoptotic peptoid nanoconjugates have also shown efficacy against AKI.[52]

Chronic kidney disease. Few studies have explored nanomedicines for the treatment of chronic kidney disease (CKD). Recent investigations have demonstrated the delivery of polycationic cyclodextrin NPs containing siRNA (siRNA/CDP-NPs) to the glomerular mesangium in mice, which could be used for the delivery of siRNA against specific targets.[53] Additionally, kidney-specific hepatocyte growth factor gene delivery using a peptide-conjugated poly(ester amine) has shown promise for the reduction of renal fibrosis in a model of obstructive uropathy.[54] In a mouse model of obstructive uropathy, treatment with chitosan/siRNA against cyclooxygenase 2 was associated with reduced severity of tubular injury and inflammation and reduced expression of proinflammatory cytokines such as tumor necrosis factor-α and interleukin-6.[55] NP-based technology also has been tested for the early diagnosis of CKD. Gold NP-based sensors were used to measure differences in exhaled air from early-stage CKD subjects as well as in animal models of CKD.[56]

Nanomaterials have the potential to improve dialysis efficacy in patients with end-stage renal disease. The use of magnetically assisted hemodialysis is a potentially promising method. In this modality, ferromagnetic NPs are conjugated to targeting moieties with high affinity for uremic toxins. Experiments using an *in vitro* system of mock dialysis demonstrated the effective removal of homocysteine with ferromagnetic NPs. This approach could potentially be used for the removal of toxins not adequately removed by conventional hemodialysis.[57,58] Additionally, polymeric antiapoptotic nanoconjugates may hold promise in the prevention of mesothelial cell injury in peritonitis, and NPs may also reduce resistant infections in peritoneal dialysis.[59,60]

The treatment of anemia associated with end-stage renal disease and CKD is also a potential use of NPs in this patient

Table 1 | Kidney disease applications of nanotechnologies, suggested and under investigation

Disease	Disease origin	Nanotechnology applications
Hypertension	Tubules and renal vasculature	Free radical scavenger,[39] vasodilator,[40] siRNA delivery[42]
Acute kidney injury	Proximal tubule	MRI imaging,[35,36] free radical scavenger,[50] thrombin inhibitor delivery[51]
Chronic kidney disease	Glomerulus and renal interstitium	siRNA[53] and small molecule delivery, detection in exhaled breath,[56] magnetically assisted hemodialysis,[57,58,61,62] resistant infections in peritoneal dialysis[59,60]
Glomerular diseases	Glomerulus	Immunosuppressive agent delivery[65–68]
Kidney cancer	Proximal tubule	Potential for targeted drug delivery

MRI, magnetic resonance imaging; siRNA, small interfering RNA.

population. Several clinical trials have shown that ferumoxytol, a superparamagnetic iron oxide NP, is more effective in improving iron levels and decreasing side effects as compared with the administration of oral or non-nanoscale iron.[61–64]

Glomerular diseases. Several experimental studies have explored the use of NPs for the treatment of glomerular diseases. The majority of these studies focus on the liposomal delivery of immunosuppressive agents. In a mouse model of IgA nephropathy, treatment with TRX20-prednisolone–loaded liposomes reduced IgA and C3 deposition to a higher degree as compared with prednisolone alone.[65] In the anti-Thy1 model of acute nephritis, TRX20 liposomes significantly reduced the glomerular cell proliferation characteristic of this model. Mycophenolatemofetil-OX-immunoliposomes have also demonstrated a benefit by reducing the severity of inflammation and extracellular matrix expansion.[66] In a mouse model of antiglomerular basement membrane, E-selectin antibody-targeted immunoliposomes resulted in a significant improvement in renal function and down-regulation of proinflammatory genes.[67] In MRL/lpr mice, a lupus nephritis model, siRNA/cationic polymer micelles reduced glomerular MAPK-1 expression and ameliorated kidney injury.[68]

Kidney cancer. The use of biodegradable polymer NPs as a strategy for the controlled delivery of drugs has shown promise for the treatment of various types of cancer including prostate, breast, hepatocellular carcinoma, colon, lung, and ovaries, among others.[17,69] Whether this strategy will also be effective in the treatment of kidney cancer has not been established. However, for the treatment of metastatic urothelial carcinoma, Abraxane (nanoparticle albumin-bound paclitaxel) was shown to be well tolerated and resulted in tumor response in 27.7% of patients, suggesting that this strategy could be an effective second-line therapy.[70]

CONCLUSIONS

The nanotechnology field holds great potential for the diagnosis, imaging, and treatment of disease. An increasingly large body of preclinical work has demonstrated the potential for addressing renal diseases. In this review, we have outlined the applications of nanomedicines and highlighted recent work in the targeting of the kidneys. We also summarized the current state of the use of nanomaterials in renal disease treatment and diagnosis, and we pointed out several nephrological areas of need. We expect to see the increasing use of nanomaterials to fill technological gaps in the treatment and diagnosis of kidney diseases.

DISCLOSURE

All the authors declared no competing interests.

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