Published in final edited form as:

Adv Healthc Mater. 2015 September 16; 4(13): 2037–2045. doi:10.1002/adhm.201500177.

Current Progress in Nanotechnology Applications for Diagnosis and Treatment of Kidney Diseases

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Abstract

Significant progress has been made in nanomedicine, primarily in the form of nanoparticles, for theranostic applications to various diseases. A variety of materials, both organic and inorganic, have been used to develop nanoparticles with promise to achieve improved efficacy in medical applications as well as reduced systemic side effects compared to current standard of care medical practices. In particular, this article highlights the recent development and application of nanoparticles for diagnosing and treating nephropathologies.

1. Introduction

Out of the many vital functions the kidney serves, electrolyte homeostasis, removal of waste metabolites from the blood, and regulation of blood pressure via the renin-angiotensin-aldosterone axis are essential to survival. ^[1] However, like other organ systems, a handful of pathologies can hinder kidney performance by either primary disease (e.g., origin of disease in the kidney itself: hereditary kidney diseases, primary renal cancer and kidney stones) or secondary disease (i.e., origin of disease in another tissue that result in kidney damage). In fact, a variety of common conditions such as diabetes and hypertension can lead to chronic kidney disease (CKD), which is generally characterized by the progressive impairment of filtering function, as evidenced by the onset of abnormal albuminuria/proteinuria. This condition alone has been documented to affect an estimated 16.8% of the US adult population. ^[2] Unlike other nephropathies that can be addressed with surgical treatments or drugs, CKD poses significant burden on global public health because it lacks any therapeutic cure other than palliative care. If preventable measures are not taken or existing disease is left untreated, CKD subsequently leads to end-stage renal disease (ESRD), advanced cardiovascular diseases, and premature death. ^[3]

Nanoparticles (NPs) are becoming increasingly attractive as a candidate tool in medicine, serving as effective diagnostic and therapeutic agents with the premise that they may reduce undesirable systemic side effects and overcome several physical and physiological barriers that systemic drug administration typically encounters. Numerous chemistries, materials, and fabrication methods can be employed to design and produce NPs with optimal functions and characteristics such as application-specific NP size and shape, prolonged half-lives in circulation, targeting to specific cell types, and multiplexing of functions (i.e., theranostics). ^[4]

In order to rationally design NP delivery systems for renal applications, it is necessary to understand the anatomy and normal physiology of the kidneys and its unique set of barriers to successful delivery. Many renal diseases accompany and result from glomerular injuries, and the crux of several nephropathies lies at the dysfunctional interface between the renal glomerulus (a capillary network that carries the blood being filtered) and Bowman's capsule (a cupping-sac surrounding the glomerulus that collects the waste filtrate from the blood into the urine) (Figure 1A). This glomerulus-Bow-man's capsule interface is where the initial and perhaps the most important step of the filtration occurs, and is incidentally often problematic in most advanced kidney diseases. For healthy individuals, only small molecules such as water, ions, and waste products pass through i) the filtration layer of the

fenestrated endothelium lining the glomerulus, ii) the glomerular basement membrane (GBM), and iii) a fine mesh called the slit diaphragm via the processes of podocytes (Figure 1B). Renal filtration occurs largely through physical and electrostatic means. Pores or fenestrae of the endothelium, 80–100 nm in diameter, provide the initial physical filtration barrier. Next, the filtrate passes through the GBM, which is negatively charged due to a high concentration of heparin sulfate and electrostatically repels negatively charged molecules and proteins from the blood. Lastly, pores of the slit diaphragm spanning podocyte processes that are approximately 15 nm in diameter finish the filtration work of the kidney. [5]

Given this landscape of the renal anatomy, the NP design features required to successfully deliver drugs to treat kidney diseases depends on the desired target within kidney architecture. This desired target is defined by the specific nature and state of the disease. For example, it may be desirable to target mesangial cells with drugs as they play a central role in kidney functions and their dysfunction is often causal in numerous nephropathologies such as ESRD. In this case, NPs would have to be small enough to pass through the fenestrae of endothelium and be negatively charged to remain within the mesangium and avoid passing through the GBM. Similarly, for targeting renal tubular epithelial cells located downstream of the glomerulus-Bowman's capsule interface that may be dysfunctional in many renal diseases, NPs would have to be small enough to pass through the slit diaphragm and possess optimal surface charge to pass through the GBM. These known criteria are crucial in designing successful NPs that target and treat renal diseases.

The rest of this review article will assess recent developments in NP systems by material type (overview given in Table 1 and NP structures shown in Figure 2) and discuss the current challenges and future directions for the development and application of nanomaterials for diagnosis and treatment of renal diseases.

2. Nanoparticle Systems for Renal Applications

2.1. Organic Nanoparticles

2.1.1. Polymeric Nanoparticles

2.1.1.1. PLGA Nanoparticles: Both natural and synthetic polymers are commonly used to fabricate NPs. In particular, synthetic polymers are widely used because their modular chemical structures allow for the precise control and tunability of NP sizes and functions. [26] One of the most commonly used synthetic polymers is poly(lactic-co-glycolic acid) (PLGA), a FDA-approved polyester proven to be an effective NP material because of its biocompatibility, biodegradability, pharmacokinetics, and potential for surface modifications to target specific cells. [27,28] Additionally, PLGA safely degrades into nontoxic monomers (i.e., lactic acid and glycolic acid) by ester bond hydrolysis. [27,29–31] PLGA compositions are usually designed by specifying the ratios of their monomers (e.g., PLGA 75:25 represents a composition of 75% lactic acid and 25% glycolic acid). For renal applications, PLGA NPs have been used in therapeutic agent delivery [7,32] and diagnostic imaging. [33] For example, Tang et al. have successfully applied PLGA NPs in plasmid DNA (pDNA) delivery. [7] The PLGA NPs were used to encapsulate pDNA embedded in calcium phosphate (CaPi), which formed CaPi-pDNA-PLGA-NPs. This NP format enhanced the

pDNA loading efficiency and optimized pDNA release kinetics, leading to increased transfection efficiency compared to conventional plasmid delivery methods (e.g., lipofectamine). While the transfection efficiency of the CaPi-pDNA-PLGA-NPs on human embryonic kidney 293 (HEK 293) cells was favorably demonstrated, further in vivo studies are necessary to confirm their efficacy in more advanced physiological settings.

2.1.1.2. PVP Nanoparticles: Other polymers used to make kidney targeting NPs include polyvinylpyrrolidone (PVP), poly[*N*-(2-hydroxypropyl) methacrylamide] (PHPMA), and copolymers containing either PVP or PHPMA as a major component. PVP is an attractive polymer for renal applications given its high solubility in both water and organic solvents, complexation capability and excellent biocompatibility as evidenced by several current FDA-approved uses. [34] Kamada et al. synthesized polyvinylpyrrolidone-*co*-dimethyl maleic anhydride [poly(VP-*co*-DMMA)] NPs that can be conjugated with amine groups of various drug molecules for renal delivery. 24 hours after intravenous administration through tail vein injection in an acute renal failure model in mice, approximately 80% of 10 kDa poly(VP-*co*-DMMA) NPs accumulated in proximal tubular epithelial cells in the kidney. Approximately 40% remained after 96 hours. This improved retention time of the NPs resulted in accelerated organ recovery from renal failure when anti-inflammatory peptides were delivered. [10] When anionic carboxyl or sulfonic groups were added to PVP to further optimize this NP system, carboxylated PVP accumulated in the kidney fivefold higher than sulfonated PVP, which was rapidly excreted in urine. Given their innate renal retention and low levels of accumulation in other organs, PVP and its anionic derivatives can be considered as excellent drug carriers for targeting proximal tubular epithelium in the kidney. [9]

2.1.1.3. PHPMA Nanoparticles: Poly(*N*-(2-hydroxypropyl) meth acrylamide) (PHPMA) is one of the most frequently used polymers for anticancer drug delivery due to its biocompatibility, water-solubility, non-immunogenicity, and its ability to enhance tumor permeability and drug retention within tumor cells. [35] M.P. Borgman et al. developed PHPMA copolymer-integrin $\alpha\beta 3$ -specific cyclo-RGD (RGDfK) with varying molecular weight and charge. This delivery vehicle was initially designed to improve targeting specificity to and aid accumulation within lung carcinomas as these tumors over-express integrin $\alpha\beta 3$. [11] Unexpectedly, when PHPMA copolymer-RGDfK was further functionalized with radioactive I ¹¹¹ chelator CHX-A''-DTPA to demonstrate a potential radiotherapeutics/diagnostic application, the PHPMA-RGDfK-CHX-A''-DTPA NPs preferentially accumulated in the kidneys instead of the lung carcinomas when administered intravenously through tail vein injection. These NPs were rapidly cleared from the blood within 1 hour and accumulated in the kidneys with minimal reduction of their accumulation over 96 hours. While the exact mechanism is unknown, the authors speculated that the increased electronegativity contributed by CHX-A''-DTPA might reduce the circulation time of NPs in the blood and increase NP accumulation in the kidney. [9,35] These results suggest PHPMA-RGDfK-CHX-A''-DTPA as a promising drug carrier for renal radiotherapy.

2.1.1.4. Chitosan Nanoparticles: Chitosan is a polysaccharide produced by alkaline deacetylation of chitin, a polymer produced by a number of biological organisms. It is

widely used as a NP material for drug and siRNA delivery because of its ideal physicochemical and biological properties such as pH sensitivity, biocompatibility, biodegradability and low toxicity. [36] Chitosan can be easily modified or combined with other polymers to improve specific functions as a NP (e.g., tissue targeting). Several methods have been approached to develop chitosan NPs for drug [12,37] and siRNA [38] delivery to the kidney. These NPs demonstrate great therapeutic potential for the treatment of various kidney diseases. In particular, the small size and negative charge of low molecular weight chitosan (LMWC)-based NPs enable efficient kidney targeting with increased uptake by renal tubular cells via megalin-mediated endocytosis. [12,39]

Incorporation of metals in polymeric NPs can provide additional advantages such as control of targeted binding interactions through metal-ligand bonds. [40] For example, when LMWC was conjugated with hydrocaffeic acid (HCA) containing catechol moieties, [12] their coordination-driven assemblies resulted in efficient NP formation with encapsulation of therapeutic agents such as doxorubicin (DOX) by controlling environmental pH. When this nanocomplex was applied for treatment of renal fibrosis induced by ureteral obstruction in mice through intravenous administration, the NPs showed exceptional stability in the circulatory system at pH 7.4, and were specifically absorbed in the proximal tubule. When these NPs were internalized into tubular epithelial cells in the kidney, low pH conditions in the endolysosomal pathway catalyzed cleavage of the NP coordination bonds and caused intracellular therapeutic release, suggesting its promising potential for use in renal cell carcinoma or fibrosis therapies.

2.1.2. Dendrimer-Based Nanoparticles—Dendrimers are nanoscale (1–100 nm) globular macromolecules with a unique architecture consisting of three distinct domains: a central core, a hyperbranched mantle, and a corona with peripheral reactive functional groups. [41] The branching number of dendrimers is referred to as the generation, which controls the NP size. Historically, dendrimers have been used for delivering drug/imaging agents because they have uniform size distribution, solubility in water, multivalency, high drug/gene loading ability, predictable release profile, and favorable pharmacokinetics. [42,43] The presence of numerous peripheral functional groups on hyperbranched dendrimers also affords efficient conjugation of targeting ligands that can bind to desired receptors, such as those over-expressed on kidney cancer cells. Presently, numerous classes of dendrimers including polyamidoamine (PAMAM), polypropyleneimine (PPI), poly(glycerol-co-succinic acid), poly-L-lysine (PLL), mela-mine, triazine, poly(glycerol), poly[2,2-bis(hydroxymethyl)propionic acid], poly(ethylene glycol) (PEG), and carbohydrate-/citric-acid-based dendrimers have been studied for drug delivery methods. [44] Among them, polyamidoamine (PAMAM) is currently one of the most extensively investigated dendrimers. [45] Due to increased positive charge on the surface from primary amine groups, PAMAM dendrimers serve as stable vectors for nucleic acid delivery. [46] However, the high surface amine density of their generations 6 or above results in high toxicity, limiting their possible biomedical applications. To address this, strategies have been proposed to either reduce the toxicity via PEGylation and acetylation or simply just using lower generations of dendrimers. [47]

Dendrimer-based NPs also show enormous potential as magnetic resonance imaging (MRI) contrast agents due to their enhanced r_1 relaxivity resulting from slow rotational dynamics as well as their tunable pharmacokinetics and labeling flexibility. Dendrimer-based MRI contrast agents can either be injected intravenously or locally. [43] PAMAM dendrimers with generations 2 through 6 and polypropylenimine diaminobutane (DAB) have been widely used as kidney-targeting MRI-contrast agents. The materials typically have small molecular weights ranging from 15 kD to 175 kD and molecular sizes ranging from 3 nm to 9 nm. [48] This size range is appropriate for kidney targeting as it allows the NPs to pass through the GBM.

2.1.3. Liposomal Nanoparticles—Liposomes, in particular cationic liposomes, are widely tested for siRNA delivery. Although cationic liposomes have shown promising efficacy in pDNA transfection, further improvements in cellular uptake and endosomal escape are required for successful translation. [16,49] Akita et al. developed a pDNA-encapsulating liposomal NPs using a cleavable disulfide bond and pH-activated lipid-like material (ssPalm) as a gene delivery system for targeting renal cell carcinoma (RCC) in flank RCC tumor xenograft model in mice through intravenous administration. [16] The tertiary amines in ssPalm act as proton sponge that disrupts endosomal membranes in acidic environment (endosomal escape), while disulfide bonds are disrupted in reducing environment (cytosol), thereby triggering release of its cargo (pDNA). [50] The surface of ssPalm NPs was functionalized with PEG to improve stability in circulation. Following intravenous injection, the PEG-ssPalm NPs accumulated in RCC tumors and showed strong anti-tumor effects by delivering pDNA encoding the soluble form of vascular endothelial growth factor receptor (VEGFR). Soluble VEGFRs bind local VEGFs and thereby prevent angiogenesis necessary for tumor growth and survival. The authors attributed the tumor targeting capability to the enhanced permeability and retention effect common in various cancers.

Hemagglutinating virus of Japan (HVJ)-liposomes are a hybrid non-viral vector system, developed by Kaneda et al. through fusion of inactivated HVJ virus particles with liposomes for gene therapy. [51] HVJ-liposomes have demonstrated faster and higher transfection rate with much lower cytotoxicity in several animal studies compared to traditional cationic lipofection. Using this delivery system, Tomita et al. demonstrated the preventative effect of gene therapy in a rat model of crescentic glomerulonephritis. Decoy nucleotides were delivered to block the activity of pro-inflammatory transcription factor NF- κ B via intrarenal arterial injection, resulting in the inhibition of damaging proinflammatory cytokine transcription. [52] Similarly, Hori et al. used HVJ-liposomes to deliver antisense nucleotides against fibrogenic TGF- β 1 in a retrograde fashion through the ureter. This treatment successfully prevented fibrosis by inhibiting TGF- β 1 in a rat model of interstitial fibrosis. [53,54] While HVJ-liposomes offer a promising gene delivery platform, some of the limitations include an inability to target specific organs such as the kidney as well as only transient gene transfection effects.

2.2. Inorganic Nanoparticles

2.2.1. Gold Nanoparticles—Metallic NPs can be derived from gold, silver, and platinum. Gold is one of the most preferred and highly utilized materials in drug delivery because it is biologically inert and structurally unique such that it can be precisely manufactured to NP sizes ranging from 1 to 150 nm. [18,55] For this class of NPs, cellular uptake typically occurs through phagocytosis, while clearance is particle-size dependent and most often occurs through hepatic or renal filtration. [56] Surface modifications made through thiol chemistry allows for application in biomarker detection, diagnostics, and drug delivery. [18,57] For instance, Marom et al. functionalized gold NPs to generate volatile organic compound-sensitive biosensors. These NPs detect CKD stage in exhaled breath samples as CKD patients are known to have increased levels of volatile organic compounds. When placed in an array form, these gold NPs alter electrical signals as volatile organic compounds bind the NPs and produce CKD stage-specific signal patterns. [17,58] Additionally, gold NPs can also serve as excellent drug reservoirs. As 100 drug molecules can bind onto the surface of a monodisperse 2 nm gold NP, this vehicle was suggested as an efficient platform for delivery of protein, nucleic acid, nitric oxide and singlet oxygen. [18,19] Many investigators have demonstrated the effectiveness of gold NPs with a particular emphasis in cancer therapy where drug release is combined with local hyperthermia to enhance tumor cell destruction. [59] When gold NPs less than 100 nm in diameter and with positive surface charge/ ζ -potential were assembled via electrostatic interactions (e.g., complexation of polycationic polymer and siRNA or DNA) and administered intravenously, they accumulated and subsequently became disassembled in the negatively charged GBM via electrostatic attraction. Coating of these gold NPs with negatively charged PEGs successfully reduced their deposition in the GBM due to charge-charge repulsion. With a controlled diameter of 75 ± 25 nm, these NPs target and accumulate most prominently in the mesangium of the kidney. These results indicate that size and surface charge are important NP design factors that can be controlled to target specific components within the renal corpuscle. [20,60]

Yet, because the metal cores are solid, they lack the ability to load drugs into a protected compartment that other organic NPs offer. Moreover, gold NPs have been shown to cause hemolysis and blood clotting. [61] Gold NPs could become much more attractive drug delivery systems if such are overcome.

2.2.2. Quantum Dot-Based Nanoparticles—Quantum dots are comprised of traditional semi-conductor materials such as zinc oxide, cadmium sulfide, and cadmium telluride. They are known to accumulate in tissues and do not easily degrade in vivo, making them an ideal agent to monitor long-term disease progression. Heavy metal-based quantum dots, however, cause toxicity by producing reactive oxygen species in cells. [61,62] This toxicity issue can be overcome by coating quantum dots with biocompatible materials like silk fibroin, which mitigated cytotoxicity and showed promise for long-term/low-bleaching in vivo imaging applications. [63] The size of quantum dots can be fabricated to range from 2.5 nm to 100 nm in diameter and coated with ligands or proteins to improve water solubility. [63,64] Cellular uptake and clearance of quantum dots occurs via endocytosis and urination, respectively. [65] Quantum dots are often used as imaging agents because i) their

fluorescence excitation and emission can be tuned to specific ranges by varying crystalline structure, size, and composition and ii) their photoluminescence is dependent on environmental factors such as pH and temperature. For example, Huang et al. developed a biosensor to detect urea in blood and urine using CdSe/ZnS quantum dots in combination with ureases. A low level of urea in urine indicates abnormal renal function. This quantum dot sensor utilized its unique capability to increase its photoluminescence upon increasing pH to accurately detect low levels of urea resulting from urea degradation by ureases in the samples.^[21]

Recently, various biomolecules (peptides, antibodies, and folate) have been conjugated to quantum dots to increase their cell targeting and internalization.^[66] In another proof-of-concept study for quantum dots as theranostics, chitosan-functionalized CdS quantum dot with an average nanocrystal size ranging from 2.2 to 3.6 nm was developed by Mansur et al. to detect and adsorb excess phosphates in hyperphosphatemia which is a known cardiovascular risk factor that commonly accompanies advanced CKD.^[67] This application leveraged the natural tendency of chitosan to bind phosphates, as well as the well-known biocompatibility of chitosan.^[22] Mansur et al. biofunctionalized CdS quantum dots through conjugating with chitosan, whose biocompatible chitosan shell binds phosphates and shields CdS core. As a result, the functionalized quantum dots could bind and adsorb phosphates. These nanoparticles can be potentially used to not only detect the areas of hyperphosphatemia in vivo, but also to take up excess phosphates to treat hyperphosphatemia. However, both short-term and long-term safety of heavy metal-based quantum dots must be demonstrated before such in vivo applications can take place.

2.2.3. Carbon Nanoparticles—Carbon NPs are synthesized most often as fullerenes, commonly known as buckyballs, or as nanotube structures. Fullerenes are one of the smallest synthesizable NPs with a diameter of around 1 nm.^[68,69] Carbon nanotubes (CNTs) are either single-walled or multi-walled (2–10 walls),^[70] and their diameters can range from 1 nm to tens of nanometers.^[71] Excretion of CNTs occurs mainly through renal clearance. Their possible applications include vaccines, small molecule transporters, biosensors and drug delivery vehicles,^[69,71,72] and several studies indicate that fullerenes may have antimicrobial properties.^[73] However, carbon-based NPs have come under scrutiny for toxicity^[74], as both single and multi-walled CNTs have been shown to induce platelet aggregation.^[61] Follow-up studies have demonstrated that these NPs can be chemically modified to improve their targeting ability and solubility in water that in turn decrease cell toxicity.^[70,71] While further investigation is required to improve the safety of in vivo CNT usage, CNTs may prove advantageous due to their high electrical conductivity, large surface area, high tensile strength, and extremely flexible architecture.^[70]

Haick et al. successfully applied CNTs for diagnosis of end-stage renal disease (ESRD). In this study, single-walled CNTs (SWCNTs) were organically functionalized to generate an array of chemiresistive random networks. This array system was used to detect subtle changes in the concentrations of volatile organic compounds in exhaled breath samples from a rat model of ESRD. To use this array system for detecting kidney diseases via breath samples, an array of 10 chemiresistive random networks of SWCNTs were coated with organic materials. The sampling system sequentially delivered ambient air and the sample

vapors to the sensors. It was found that the sensor of the array underwent a reversible change in electrical resistance when exposed to a vapor or analyte, indicating the potential to detect small concentrations of organic compounds observed in the breath of ESRD patients. [23] As mentioned earlier, this line of work from Haick et al. continued with gold NPs to further demonstrate the application of NPs for detection of volatile organic molecules in breath samples.

2.2.4. Magnetic Iron Oxide Nanoparticles—Significant progress has been made in developing functional and molecular imaging modalities due to advances in nanoscale probing technologies. The use of iron oxide NPs as MRI contrast agents is considered as one of the most successful bio-medical applications of inorganic NPs, reflected by a number of iron oxide-based contrast agents that have been approved by the FDA to date. [75] MRI contrast agents including iron oxide NPs work similarly by shortening relaxation time in the surrounding tissues due to the magnetic susceptibility effect from the magnetic agents. Iron oxide NPs are classified into two categories based on size: ultra-small particles of iron oxide (USPIO, diameter < 40 nm) and small particles of iron oxide (SPIO). The difference in their particle size leads to different in vivo uptake processes. Larger SPIO NPs accumulate mostly in the liver and spleen while smaller USPIO NPs are taken up by inflammatory cells/lymph nodes. [76] Hence, iron oxide NPs can be used to monitor various anatomical features as well as organ functions such as glomerular filtration rate. [77] Moreover, USPIO NPs can be used for labeling stem/progenitor cells. For example, Ittrich et al. demonstrated in vivo tracking of SPIO-labelled mesenchymal stem cells that were injected intraaortally for treating acute ischemic kidney injury in rats. [24] Although the safety of long-term frequent use of iron oxide NPs remains to be examined, infrequent iron oxide NP usage for MRI appears to be well-tolerated with little to no reported side effects. [78]

Currently, clinical assessment of renal inflammation can only be done by renal biopsy. However, MRI with iron oxide-based NPs has been successfully used in animal models via intravenous administration for detection of various nephropathies that accompany specific patterns of inflammatory cell distribution within the kidney. [79] When USPIO NPs were administered, inflammatory cells took up these NPs, and thus the T2-weighted MRI signal decreased in these areas of high inflammatory cell population due to magnetic susceptibility. [80] For instance, anti-GBM glomerulonephritis with inflammatory cell recruitment at the cortical region of the kidney can be diagnosed by USPIO NPs through large changes in MRI signal intensity in the cortical region. On the other hand, with ischemia-reperfusion injuries, MRI signal reduction was located exclusively in the medullar region. [81] It was also shown that nephrotic syndrome and renal graft rejection led to overall reduction in the MRI signal intensity throughout the kidney. [82] The small size of USPIO allows easy passage of NPs in the kidney, and their uptake by inflammatory cells and the resulting pattern permit accurate non-invasive diagnosis.

Another interesting application of iron oxide NPs is intravenous iron therapy. Ferumoxytol is an FDA-approved USPIO drug for treating CKD/ESRD-associated anemia. [83] It is designed to have a superparamagnetic iron oxide core coated with branched polysaccharides, offering superior stability in circulation with blood flow. When internalized by macrophages, iron is released and becomes available to be incorporated into hemoglobin to facilitate

erythropoiesis. Owing to its superparamagnetic iron oxide core, ferumoxytol is increasingly used as an MRI-enhancing agent for imaging lymph nodes, tumors, and vascular lesion. It is also considered as a promising alternative to replace nephrotoxic gadolinium-based MRI contrast agents. [84]

3. Current Challenges and Future Directions

This review highlights the current use of various organic and inorganic NPs for the diagnosis and treatment of kidney diseases. Though the field is nascent, an increasing number of studies are combining promising NPs and multi-faceted targeting strategies to establish better treatment and diagnosis options for renal disease patients. Considering the natural convergence among the fields of nanotechnology, kidney biology, and nephrology, collaborative efforts among researchers in these fields should aid progress. Indeed, recent studies in the fields of basic renal physiology and pathophysiology are identifying better targets and new potential barriers to these targets for delivering drugs/NPs. In particular, podocytes have gained immense interest in the field of nephrology in the last 15 years. Previously, it was thought that the GBM offered the primary structure and mechanism for filtering waste molecules and retaining plasma proteins. However, recent studies have identified causal genes associated with slit diaphragm/podocytes for nephrotic syndrome and have also shown that blocking of slit diaphragm proteins led to massive proteinuria, emphasizing the importance of podocytes and their processes/slit diaphragm in renal function. [85] Electron microscopy has revealed that the ≈ 15 nm openings of slit diaphragm scaffold are responsible for retaining plasma proteins and preventing proteinuria. [5] With these recent findings, it is now well-accepted that podocytes play a key role in renal filtration and basic kidney functions, and that podocyte dysfunction, injury, and loss are likely to be the cause in 90% of ESRD. [86] Therefore, designing nano-medicines that can target and deliver therapeutics specifically to podocytes could have a sizable impact in treating numerous kidney diseases. This remains a relatively unexplored, yet important venue for tackling renal diseases.

The development of imaging agents is another promising area for renal disease nanotechnology. One of the most pressing needs that require immediate innovative solutions is the ability to monitor kidney functions of patients at advanced stages of renal diseases. Traditionally, iodinated computed tomography (CT) or gadolinium MRI contrast agents have been used to monitor kidney status. However, such agents suffer from rapid renal clearance and occasional nephrotoxicity due to the high concentration required for imaging. Various NPs containing iodinated compounds, iron oxide, or other heavy metals (i.e., quantum dots) could be modified to improve circulation time and to reduce loading doses, as was discussed earlier. Nonetheless, exposure to these metal NPs could be cytotoxic and inflammatory, [87] and also induce side effects in the kidney such as tubular cell damage. [88] Therefore, the safety and potential complications of applying NPs need to be thoroughly and carefully addressed in order to bring NP contrast agents closer to clinical translation.

Even though significant challenges and issues remain to be addressed, the potential impact of NPs on the diagnosis and treatment of kidney pathologies is widely recognized. As suggested through several examples in this review, careful modification and characterization

of NPs are greatly needed in order to maximize the potential impact of the nanomedicine field to advance kidney disease treatments and early diagnosis.

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Figure 1.

Renal Anatomy. A) Kidney consists of nephrons, the basic filtering units. Adapted with permission.^[89] Copyright 2015, UNC Kidney Center. B) Glomerulus is a network of capillaries carrying blood to be filtered in renal corpuscle, and is surrounded by the Bowman's capsule. Waste must pass through the three filtration layers: fenestrae of the endothelium, glomerular basement membrane, and slit diaphragms between the processes of podocytes. Adapted with permission.^[6] Copyright 2008, Nature Publishing Group.

Figure 2. Schematic representation of various A) organic and B) inorganic nanoparticles. Adapted with permission. ^[25] Copyright 2013, Wiley & Sons.

Table 1

Studies on kidney targeting by polymeric and inorganic nanoparticles.

Category	Materials	Characteristics	Target	Ref.
Polymeric NPs	PLGA	Calcium phosphate embedded for plasmid(p)DNA delivery	Kidney disease	[7]
		Covalently loaded tetraiodothyroacetic acid in PLGA NPs	Renal cell carcinoma	[8]
		Anionized PVP derivatives (Copolymers of carboxylated PVP and sulfonated PVP)	Renal disease	[9]
	Poly vinylpyrrolidone (PVP)	Polyvinylpyrrolidone-co-dimethyl maleic anhydride [poly(VP-co-DMMA)], drug delivery	Acute renal failure	[10]
		HPMA-RGDfK conjugates of various molecular weights	Kidney	[11]
	Chitosan	Catechol-derived low molecular weight chitosan/ Doxorubicin	Renal fibrosis	[12]
		50% N-acetylated low molecular weight chitosan (LMWC)	Renal disease	[13]
		PAMAM/MRI contrast agents	Kidney imaging	[14]
	Dendrimer	PAMAM-G4/Drug delivery	Renal disease	[15]
		pDNA-encapsulating/pH-activated	Renal cell carcinoma	[16]
	Liposome	Nanoparticle arrays as biosensor	Chronic kidney disease	[17]
		Monodisperse 2 nm NPs: Protein, nucleic acid, nitric oxide and singlet oxygen delivery	Drug delivery for kidney diseases	[18,19]
	Gold	Negatively charged PEGylated nanoparticles (20–170 nm)	Kidney cancer	[20]
		CdSe/ZnS quantum dots and urease	Renal function	[22]
		Chitosan functionalized CdS quantum dot	Renal diseases/Failure	[22]
Inorganic NPs	Carbon	An array of chemiresistive random networks of organically functionalized single-walled carbon nanotubes	End-stage renal disease	[23]
		Ultra-small particles of iron oxide for labeling stem/progenitor cells	Acute ischemic kidney injury	[24]
	Magnetic Iron Oxide	Ultra-small particles of iron oxide for MRI	Renal disease	[24]