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Applications of Nanoparticles in the Detection and Treatment of Kidney Diseases

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Abstract

Nanoparticles have emerged in the medical field as a technology well-suited for the diagnosis and treatment of a variety of disease states. They have been heralded as efficacious owing to both in terms of improved therapeutic efficacy as well as reduction of treatment side effects in some cases. Various nanomaterials have been developed which can be tagged with targeting moieties, and with drug delivery and imaging capability or combination of both as theranostic agent. These nanomaterials have been investigated for treatment and detection of various pathological conditions. The emphasis of this review is to demonstrate current research and clinical applications for nanoparticles in the diagnosis and treatment of renal diseases.

Keywords

nanoparticles; kidney disease; targeting; treatment; review

Introduction

The field of nanomedicine is rapidly progressing and widely expanding. Nanoparticles (NPs) have been investigated for numerous medical applications and are showing potential as a delivery method for diagnostic and therapeutic agents. Particularly, it is believed that NPs may be able to overcome certain biological and physical barriers where conventional therapies fail. NPs are colloidal dispersions consisting of an inner core and an outer shell, or a matrix structure that can encapsulate a drug, protein, imaging agent, or combination of therapeutic and imaging agents in a single nanostructure. Particle size is typically between 100 nm and 300 nm, although many formulations and applications call for smaller sizes. The agent of interest can be bound to the surface of NPs or encapsulated, allowing for delivery of therapeutics that would be otherwise unstable, insoluble, or biologically inactivated under typical conditions.

NPs for biological applications must be constructed in a way that they possess favorable characteristics when applied to cells, tissue, or serum. NPs inherently have a high surface

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area to volume ratio due to their small size. This results in a natural tendency to aggregate and interact with plasma proteins upon intravenous injection, leading to rapid clearance by the reticuloendothelial system (RES). Thus, NPs are often coated with hydrophilic and biocompatible polymers, such as polyethylene glycol (PEG) or pluronics, which protect against opsonization and endocytosis, and afford an extended plasma half-life^{1–3}. The manipulation of these coating materials and size of the NP in turn alters the drug release profile and drug concentration delivered.

Oral route of drug delivery is often hampered by absorption, local toxicity, enzymatic degradation and solubility in the gastrointestinal system. Polymeric NPs have been actively explored as oral delivery vehicles for pharmaceutically challenging molecules⁴. It has been shown that NPs can improve the oral bioavailability of drugs that have poor water solubility and high molecular weight⁵. This can be achieved by modifying both the physicochemical properties and by coupling targeting molecules to the NP surface⁶. Hydrophilic polymers such as PEG and chitosan have been shown to enhance delivery across the intestinal mucosa^{7,8}. Proteins, vaccines, and nucleic acid material have shown promising results for oral delivery and all have potential applications to kidney disease.

Along with their physicochemical properties helping NPs evade certain biological barriers, NP surfaces can be manipulated to target end organs or tissues via the surface polymer charge, shape, or conjugated ligand. Methods have been developed to make NPs hydrophobic or create electrostatic charges, which improve site-specific delivery⁹ (Figure 1). NPs can be manipulated also by conjugation of specific ligands to the surface of the particle in the attempt to target a specific site, including antibodies and peptides which target specific cell receptors. For example, tumor cells express various molecular markers not expressed on normal tissue, which can be used as docking sites to concentrate drug loaded NPs to tumors¹⁰. Furthermore, the vasculature endothelium of tumor cells can be targeted to enhance NP delivery and take advantage of the tumor enhanced permeability and retention effect¹¹ (Figure 2). Table 1 summarizes the characteristics and targets of various NPs created and being studied for treatment of renal diseases.

The vast range of diseases affecting the kidney often requires both a medical and a surgical treatment course. The diverse research and applications of NPs in the field of kidney disease alone has opened new avenues of treatment, disease detection, and disease monitoring. Problems are acute and chronic in nature and often involve a nephrologist and urologist. Here we explore the growing field of NPs in various kidney diseases and their experimental as well as clinical applications and why the practicing clinicians should have knowledge of this new technology (Figure 3).

NPs in Renal Targeting and Renal Imaging

The kidney is a unique organ for targeting of NPs due to its innate ability to rapidly clear particles that are smaller than 10 nm in diameter¹². This is accounted for by the glomerular filtration unit, the basement membrane, and the interdigitating podocytes. Within the renal corpuscle, there exists a fenestrated endothelium separating the mesangium from the extracellular matrix. Therefore, 2 nm particles are readily cleared by the kidney, but significantly decreased when size is 6 nm and virtually no renal excretion at 11 nm diameter¹³.

Choi et al devised gold-loaded nanoparticles of serial core diameters entrapped by PEG polymer of various sizes¹². They demonstrated that NPs of 80–100 nm target the mesangium of the kidney, where smaller particles are seen only in the peritubular capillaries and the largest particles are taken up by the Kupffer cells in the RES of the liver and spleen.

Another method of NP targeting involves immunotargeting. NPs can be created such that functional groups on the exterior can be easily conjugated to a broad range of biological molecules such as proteins or peptides. NPs tailor made that encapsulate imaging contrast agents, such as iron oxide when deployed with MRI, make it possible to diagnose, track disease, track cells and tissues, and deliver of therapeutics^{14–16}. By combining these approaches of immunotargeting and encapsulation of a contrast agent, Hultman et al used major histocompatibility complex (MHC) anti-MHC II antibodies as a marker of adaptive immune response and inflammation to target the renal medulla of the rat³. This is thought to be more specific than simply targeting macrophages which nonspecifically accumulate at sites of inflammation. They show a five-fold longer half-life in the renal medulla specifically with MHC II antibody conjugated iron oxide NPs than non-conjugated NPs³. The ability to target a specific compartment of the kidney has implications for delivery of therapeutics as well as monitoring disease states affecting different portions of the kidney.

The kidney has been targeted with magnetic NPs as well. Magnetic NPs work by applying an external magnet near the target region to localize the magnetic field¹⁷. In a proof of concept study, Kumar et al demonstrated fluorescent magnetic NPs could be selectively delivered to the kidney in a mouse model more so than non-magnetized particles¹⁸.

NPs for Renovascular Hypertension

Free radicals play a role in cardiovascular disease and antioxidants are being explored for their benefits in reducing the oxidative stress pathway¹⁹. Agents targeted at free radical scavenging have not been previously used in treatment of cardiovascular disease due to poor physicochemical and biopharmaceutical properties leading to low oral bioavailability¹⁹. One such free radical scavenger, coenzyme Q10 (CoQ10), plays a critical role in cellular respiration in the mitochondria as well as functions as an antioxidant, free radical scavenger, and inhibitor of lipid peroxidation²⁰. CoQ10 has been found to be effective in cardiovascular disorders like cardiomyopathy, hypertension, angina pectoris and atherosclerosis, as well as cardiotoxicity caused by doxorubicin^{21,22}. Clinical trials have demonstrated the potential of CoQ10 in treatment of hypertension in humans by means of decreasing total peripheral resistance and therefore resulting in vascular wall relaxation²³. CoQ10 also acts as an antagonist for vascular superoxides, either scavenging them or suppressing their synthesis²⁴.

To overcome the hurdles of drug delivery of CoQ10, PLGA formulated NPs have been synthesized to increase oral bioavailability and establish a therapeutic effect of CoQ10¹⁹. A Goldblatt 2 kidney 1 clip model was used for induction of hypertension in a rat model. CoQ10 encapsulated NPs were injected intravenously for 12 days and the experimental animals showed a significantly reduced blood pressure as compared to suspended CoQ10 and at 60% lower dose¹⁹. This shows the efficacy of CoQ10-NPs at blood pressure reduction and potential as a therapeutic for humans.

Another area of research has examined the antihypertensive properties of cytochrome P450 metabolites. One such metabolite is epoxyeicosatrienoic acid, which has been shown to demonstrated vasodilatory properties in vascular beds independent of nitric oxide or prostaglandins²⁵. However, epoxyeicosatrienoic acid is readily cleaved to its less active diol form by epoxide hydrolase²⁶. 1,3-Dicyclohexyl urea (DCU) is a potent soluble epoxide hydrolase inhibitor and has been shown to lower systemic blood pressure but can only be given intraperitoneally in rat models due to its poor aqueous solubility²⁷. Ghosh et al sought to increase solubility and bioavailability by creating a DCU nanosuspension, which increased surface area 40-fold and enhanced oral bioavailability²⁸. Furthermore, they were able to show a significant difference in a hypertensive rat model in both angiotensin II levels

as well as decreasing systolic pressures by nearly 30 mmHg²⁸. Improvement in drug oral bioavailability would have wide application for treating patients on a chronic outpatient basis.

Atherosclerosis is closely associated with hypertension and the proportion of patients with lesions and hypertension is higher than those with normal blood pressure²⁹. The renin-angiotensin-aldosterone system (RAAS) plays an integral role in hypertension and is closely related to and affected by atherosclerosis. Angiotensinogen, a precursor to angiotensin I, has been found to be significantly elevated in hypertensive patients³⁰. Embracing these principles, Lu et al created nanoparticles loaded with silencing RNA (a short hairpin RNA) against angiotensinogen for the treatment of a hypertensive rat model³¹. They found the mRNA expression of angiotensinogen in the liver of treated rats was markedly reduced compared to control groups and, furthermore, the systolic blood pressure was reduced by an average of 27 mmHg compared to pretreatment levels. Moreover, histological examination of major vessels indicated that the inflammatory changes associated with atherosclerotic plaques were attenuated after treatment as well³¹.

NPs for Acute Renal Failure

Acute renal failure (ARF) is life-threatening, occurs in up to 20% of intensive care unit patients, and carries a high mortality rate³². Early diagnosis and initiation of therapy is necessary for reducing morbidity and mortality. ARF has numerous causes including hypotension/sepsis, trauma, acute tubular necrosis (ATN), pharmaco-toxins causing acute interstitial nephritis (AIN), contrast injury, and urinary obstruction.

Current diagnosis of ARF requires serum blood tests and commonly examines blood urea nitrogen (BUN) and creatinine levels. Problems with these tests are numerous, including the non-specific/diagnostic nature of the tests and the delay in rise in these elements can be up to 24 hours³³. One method for detection of ARF that has been explored uses a dendrimer nanoparticle-based magnetic resonance imaging (MRI) technique^{34,35}. A dendrimer is a repetitively branched molecule that often takes the form of a sphere with symmetry established around a core with functional groups at the surface. An array of dendrimer nanoparticles were used to examine their ability to detect even short amounts of ischemia in a mouse model and found that the size of the poorly enhanced area of kidney correlated with the duration of ischemia and reperfusion time³⁴. Again, in a mouse model of sepsis induced ARF, it was shown that dendrimer-encapsulated contrast NPs coupled with MRI could detect renal injury before serum creatinine became elevated³⁵. This has implications for potential early institution of therapy or removal of nephrotoxic elements before kidney damaged is detectable in the serum.

In an animal model of acute tubular nephrotoxicity cause by cisplatin, MRI was used to study changes in medullary enhancement³⁴. It was observed that imaging with dendrimer-coated NPs was able to distinguish medullary enhancement loss after tubular injury when normal phase MRI could not. Signal loss on NP enhanced MRI was proportional to the degree of renal damage³⁴.

Differentiation of kidney disease can also be a diagnostic challenge, often relying on renal biopsy, which is invasive and has potential for complications. Macrophage activity in the normal state is virtually absent in the kidney, but it occurs frequently in nephritis, renal transplant rejection, and renal obstruction^{36–38}. Hauger et al sought to determine if macrophage activity could be imaged and localized to compartments of the kidney based on disease type. In a rat model, ultrasmall superparamagnetic iron oxide (USPIO) NPs 4–6 nm in diameter and coated with dextran were injected into a nephrotoxic nephritis model (anti-basement membrane, equivalent to Goodpasture syndrome) or into an obstructive nephropathy model, which induces diffuse interstitial lesions throughout the kidney. MRI

signal intensity with the NPs loss localized in the cortex (where glomerular lesions occur) in the nephritis model and localized to the entire kidney in the obstructive model. Furthermore, the degree of signal intensity loss was correlated to the degree of proteinuria in the nephritis model.

Urinary or ureteral obstruction has been implicated in the processes of acute interstitial renal disease and inflammation. In an animal model, unilateral renal obstruction has been shown to cause an increase in the collagenous fibrous tissue in the renal interstitium after 6 days from time of injury³⁹. This effect was able to be visualized with the aid of silica loaded nanoparticles in the following model. Taking advantage of the inflammatory cascade, fluorescent anti-CD11b nanoprobes were designed (CD11b is expressed on the surface of mouse macrophages) and injected intravenously into a mouse model of unilateral ureteral obstruction. The NPs were accumulated in the UUO kidney to a significantly greater extent compared with the normal, non-inflamed kidney³⁹.

NPs for use in Renal Transplantation and Ischemic-Reperfusion Injury

Renal ischemic is a reduction of cortical blood flow causing tissue hypoperfusion that can be caused by disease states such as sepsis, hypotension, or renal artery stenosis (RAS) or iatrogenically such as after partial nephrectomy or during renal transplantation. After renal ischemia, renal blood flow returns toward normal but regional alterations occur. The outer medullary region is marginally oxygenated under normal conditions and has high energy demands, specifically the thick ascending limb of the renal tubule^{40,41}. The blood flow to this region after reperfusion amounts to ~10% of normal, leading to regional congestion due to edema, poor blood flow, deprivation of nutrients and loss of ATP⁴². ATP degradation products such as hypoxanthine can leak out of cells and can be converted by xanthine oxidase to uric acid and form reactive oxygen species in the process, contributing to ischemic damage⁴¹. Tubular cell swelling in the confined space of the outer medulla mechanically adds to capillary obstruction and causes medullary congestion, decreased medullary blood flow, and further perpetuating ischemia and tubular cell injury⁴¹.

A recent study suggests that permanent damage to peritubular capillaries occurred in rats that underwent renal ischemia and may partly account for the pathogenesis of chronic renal failure in this setting⁴³. Renal ischemia leads to cell necrosis by generation of breakdown products of cell energy such as ROS, increase in free cytosolic calcium, and activation of phospholipases, proteases, and endonucleases^{41,44}. Cellular debris and intratubular protein from casts and obstruct the tubules, causing increased pressures proximal to the obstruction; the fluid that leaks out from the obstructed tubules causes tissue edema⁴¹. The oxygen burst phenomenon is a trigger for complex biochemical reactions leading to generation of oxygenated lipids and changes in microcirculation with recruitment of neutrophils after reperfusion of a transplanted organ⁴⁵.

Agents such as mannitol that inhibit cell swelling partially protect the kidney against the functional deficits induced by ischemia and also decrease medullary congestion⁴⁶. Scavengers such as SOD, glutathione, and vitamin E, as well as inhibitors of ROS production, such as the iron chelators (e.g. deferoxamine) have been reported to protect against ischemic injury^{47,48}.

Two molecules that have been widely studied and implicated in ischemia-reperfusion injury include endothelin and nitric oxide, which regular vascular tone and may affect leukocyte adhesion⁴⁹. Nitric oxide may decrease adhesion of epithelial cells enhancing ischemia-reperfusion injury by increasing the detachment of tubule cells resulting in intraluminal obstruction⁴⁹. The inflammatory response may be implicated in renal injury as leukocytes infiltrate and cause edema by compromising microvascular blood flow⁵⁰. Tubule segments

in the outer medulla, especially the proximal tubule, are most susceptible to injury given its limited capacity to undergo anaerobic metabolism in the setting of a decrease in oxygen tension⁴⁹.

ROS are toxic to tubular epithelial cells and scavengers such as superoxide dismutase, glutathione and vitamin E, and inhibitors of ROS production, such as desferoxamine, have been reported to protect against renal injury^{47,48}. Ischemia-reperfusion produces excessive ROS that are unable to be handled by the tissues normal scavenging system⁵¹. Excessive ROS leads to cell damage by lipid peroxidation, DNA breakdown, and protein damage. ROS have been implicated as contributors to chronic allograft loss following transplantation due to development of renal fibrosis through loss of epithelial cell membrane transporters and their functions and the acquisition of a more fibroblastic phenotype leading to production of extracellular matrix elements such as collagen and fibronectin⁵¹. Superoxide dismutase (SOD) appears to be the most important enzymes involved in the defense system against reactive oxygen species⁶, particularly against superoxide anion radicals⁵². Delivery of superoxide dismutase to the sites of potential free radical injury has been shown to reduce fibrosis in animal models⁵¹.

The therapeutic utility of antioxidants is hindered by inadequate delivery due to short intravascular half life and susceptibility to proteolysis⁵³. NPs for delivery of SOD have been explored but not yet specifically in the kidney. Chen et al created silica NPs containing SOD and conjugated them to a transactivator protein (TAT) to enhance intracellular delivery⁵⁴. SOD NPs have been utilized in a stroke model as well⁵⁵. Yun et al showed that SOD loaded NPs reduced neuronal cell death in vitro and in a mouse model, SOD NPs reduced stroke volume by 50%, reduced inflammatory markers, and improved mouse neuronal function post-injury^{55,56}.

Monitoring renal allografts after transplantation is a necessary part of long term care. Specifically early detection of graft rejection and institution of therapy may provide increased longevity of graft survival and decrease morbidity of ESRD. Although numerous techniques have been used for the detection of graft rejection, development of specific, sensitive, and non-invasive methods for the diagnosis of rejection is still a major challenge in the field of renal transplantation⁵⁷. Renal biopsy, the “gold standard” for rejection diagnosis, can be complicated by hemorrhage, infection, and arteriovenous fistula (AVF). MRI has the potential to be utilized for early detection of allograft rejection when coupled with dextran-coated superparamagnetic iron oxide nanoparticles^{57,58}. These particles have previously been utilized as a vascular contrast agent as well as to detect macrophage infiltration into the kidney^{59–61}. As renal allograft rejection is histologically marked by infiltration of T-cells and most strongly with persistence of macrophages, a method of monitoring this process would aid in the treatment of rejection. Ye et al was able to demonstrate in a rat model a predictable and significant difference between MR signal intensity in the renal cortex of renal grafts with iron oxide nanoparticles in allografts as compared to isografts⁵⁷. This could be a valuable and noninvasive method of detecting acute rejection.

Cyclosporine (CsA) is a first-line immunosuppressant used to prevent graft rejection and in treatment of autoimmune disorders. Until the recent production of the drug Neoral, CsA manufacturing has been associated with low or variable oral bioavailability⁶². Nephrotoxicity is a significant challenge to overcome with new formulations of CsA. Efforts have been made to create nanoparticulate formulations of CsA to improve bioavailability as well as reduce toxicity^{63,64}. PLGA-full form NPs were prepared at different loading concentrations and tested in a rat model at different doses to examine toxicity and tissue levels for 30 days¹⁹. It was shown that NP formulation at 30 mg/kg and 30% loading

produced a similar maximal concentration of CsA with significantly lower nephrotoxicity. Additionally, they observed smaller fluctuations of blood CsA concentrations over 30 days than with Neoral due to the sustained NP release effect¹⁹. Drug preparation for immunosuppression will continue to be a major portion of renal transplant patient care.

NPs in Chronic Kidney Diseases

Chronic kidney disease (CKD) is a progressive loss of renal function over months to years marked by a loss of glomerular filtration capability. In CKD, toxins, which would otherwise be excreted by the normal functioning kidney, are able to accumulate in the blood. Following creatinine and BUN levels for CKD have the short-comings of varying with age, gender, diet, muscle mass, muscle metabolism, medications, diet and hydration status⁶⁵. However, much of kidney function can be lost before accumulation of toxins in the blood can be detected, leading to late diagnosis and treatment of CKD.

A novel method for identifying CKD and disease progression has been explored that utilizes breath testing of volatile organic compounds (VOCs)⁶⁶. Work by Haick et al demonstrated a non-invasive means of detecting end-stage renal disease (ESRD) in a rat model based on a carbon-nanotube-based sensor and breath sample analysis⁶⁷. The work was then continued with a focus on identification of early-stage CKD in which patients with CKD had breath analysis performed with gold nanoparticle sensors. The NP coated sensors acted to extract the VOCs from breath samples, which could then be analyzed by gas chromatography. The results showed that a combination of gold NP sensors could distinguish with high accuracy between the exhaled breath of early-stage CKD and healthy states, advanced and end-stage CKD, as well as ranges in between⁶⁸. This technology has the possibility to improve screening methods for CKD and early detection and treatment.

Magnetically assisted hemodialysis (MAHD) has been proposed as a more efficient means of management of ESRD. In MAHD, biocompatible ferromagnetic NPs are bound to targeted binding substances which have high affinity for serum toxins in the body. The binding substances proposed for utilization could be proteins, immunoglobulins, or antibodies. Body areas can then be targeted with magnetic manipulation of the iron component of the NPs. The proposed system would function by infusion of the NPs prior to HD session, thus, allowing adequate time for the binding on NPs to toxic substances prior to the actual HD session. The study evaluated the toxin homocysteine and demonstrated that it was readily absorbed onto the targeted carriers and then cleared rapidly in *in vitro* studies⁶⁹. Furthermore, they were able to demonstrate that after one circulation of blood volume, only an immeasurably small magnetic signal remained in the blood. This is compared to the required roughly 8 circulations of blood volume in current HD therapy. The implication is the MAHD would achieve improved clearance of toxins in a shorter period of time improving the quality of life of ESRD patients.

Nephrologists frequently treat anemia associated with chronic kidney disease. Anemia in CKD patients results from a lack of production of erythropoietin by the kidneys. Furthermore, CKD is an inflammatory condition leading to sequestration and impaired release of iron from macrophages of the RES in the liver, spleen, and bone marrow, or reticuloendothelial blockade⁷⁰. Hepcidin, a compound produced by the liver during inflammation, inhibits oral iron absorption in the small intestine and thus limits bioavailability of conventional oral therapy⁷¹. Ferumoxytol is a superparamagnetic iron oxide nanoparticle that has a polyglucose carboxymethylether coating and a particle diameter of 30 nm and molecular weight of 731kD⁷². There are several Phase III clinical studies regarding the treatment efficacy of ferumoxytol with patient both prior to initiation of HD and those receiving long-term HD which demonstrate that compared to oral iron

therapy, ferumoxytol given intravenously causes a significantly greater percentage of patients to achieve a 1g/dl increase in hemoglobin blood values^{73–75}. With similar adverse events compared to oral therapy, the NP preparation of ferumoxytol has been shown to be an efficacious treatment for iron deficiency anemia associated with CKD.

In chronic inflammatory diseases of the kidney such as lupus nephritis, the degree of renal involvement varies and currently there exist no urine or serum biomarkers that predict biopsy results for severity of involvement^{76,77}. Examination of renal tissue for C3 fragment deposition within the glomeruli is a routine part of the evaluation of renal biopsies, and tissue C3 deposits are interpreted as evidence of complement activation⁷⁷. Imaging of antibodies in immune complexes relative to circulating antibodies is unlikely to be useful, given the small differences in antibody concentration between the blood pool and deposits when averaged over imaging voxels⁷⁶. However, targeting cleavage products of the complement system with nanoparticles enables the focus on tissue-bound fragments rather than circulating intact complement and provides a target for imaging. Serkova et al have developed an animal model of nephritis and used targeted magnetic resonance imaging with nanoparticles to monitor progression over time⁷⁸. Antibodies to the cleavage product of C3 (C3d) were encapsulated in magnetic NPs, allowing monitoring of changes in inflammation in the kidney by MRI⁷⁸. This type of non-invasive, organ specific monitoring potentially allows titratable treatment of disease to preserve renal function even prior to detection of renal deterioration by serum chemistry testing.

Half of all Americans have CKD over the age of 70 and nearly 25% of patients undergoing angiography studies have CKD⁷⁹. For these patients, iodinated contrast or gadolinium based contrast could mean worsening of disease to the point of needing renal replacement therapy, or could be fatal with gadolinium and nephrogenic systemic fibrosis (NSF)¹. Magnetic NP imaging is a safe modality for these situations and uses superparamagnetic iron oxide NPs to localize the spatial position of the NPs with nearly no background tissue noise⁸⁰. These iron oxide particles are processed and stored in the liver with the body's iron reserve to be used in hemopoiesis and do not affect the kidneys⁸¹.

NPs for Neoplasms of the Kidney

Imaging

Metastatic renal cell carcinoma (RCC) is nearly always a fatal disease. These highly vascular tumors are chemo- and radio-resistant and thus current treatment regimens consist of vascular targeting agents, such as tyrosine kinase inhibitors (TKIs), vascular endothelial growth factor (VEGF) inhibitors and mammalian target of rapamycin (mTOR) inhibitors, which help slow disease progression. After institution of therapy, patients are followed clinically with axial imaging either computed tomography (CT) or MRI. Size of tumor serves as a surrogate to tumor response to treatment. MRI approaches using magnetic NPs have recently been validated for the examination of tumor vascularity in vivo⁸². Therefore, Guimaraes et al examined a mouse model for RCC and followed tumor vascularity change using magnetic NPs after treatment with both mTOR inhibitor and TKI⁸³. The study observed marked reduction in tumor vascularity in both groups from baseline and control untreated groups of animals. The advantage to this potential monitoring technique would be measuring response to therapy, act as a surrogate biomarker of anti-angiogenic therapy. NP imaging targeting tumor vascularity could serve as a preclinical outcome measure of dose scheduling, and allow for pretreatment determination of potential therapeutic efficacy with those tumors demonstrating low vascular volume fraction, possibly precluding anti-angiogenic treatment strategies^{82,83}.

An unusual application of NPs for renal imaging has been reported in a case of splenosis⁸⁴. A patient, who formerly underwent splenectomy, was found to have a left renal mass on cross sectional imaging. Using ferumoxide, dextran-coated superparamagnetic iron oxides preferentially taken up by Kupffer cells of the RES, the kidney parenchyma was able to be distinguished from the ectopic autotransplanted splenic tissue. This is evident by loss of signal on T₂-star imaging⁸⁴. The patient was spared from undergoing nephrectomy.

Metastatic treatment

Cytokine therapy with interleukin-2 or interferon-alpha have been standard of care for many years for treating metastatic RCC and have response rates of ~15%⁸⁵. 2-methoxyestradiol (2ME2) is a non-estrogenic derivative of estradiol with antiproliferative and antiangiogenic activity that downregulates hypoxia inducible factor alpha (HIF-1 α)⁸⁶. The capsule formulation of 2ME2 showed minimal plasma levels and could not be evaluated for therapeutic potential⁸⁷. NPs of 2ME2 were created and have undergone investigation in a Phase I trial in patients with metastatic RCC who progressed on a TKI⁸⁸. Because of the response of several patients, a Phase II study was undertaken with 17 patients either receiving 2ME2 NPs alone or in combination with sunitinib. No observed objective response was demonstrated at the recommended dose and a significant number of patients required discontinued treatment due to toxicities⁸⁶.

Gene therapy is an active area of cancer research, offering the ability to target the base cause of cancer regulating genes. However, one challenge of gene therapy is delivery *in vivo* as DNA and RNA typically have short half-lives in circulation⁸⁹. The encapsulation of nucleic acids by PEG offers protection *in vivo* from enzymatic and immune mediated degradation and increases their size, preventing renal clearance⁹⁰. As metastatic RCC is not sensitive to radiotherapy or chemotherapy, immunomodulation and gene therapy have been targets of new research. Gene therapy has been investigated using polyethyleneimine (PEI) as a delivery system in nanocomplexes through electrostatic interactions with DNA. However, the PEI is cytotoxic to the point of ineffectiveness⁹¹. Xu et al evaluated 3 modifications of PEI in terms of cytotoxicity and transfection efficacy in an RCC mouse model⁹². They found that all modified nanoparticles had lower cytotoxicity compared to PEI and furthermore one (a folic acid modified NP) had improved transfection efficiency *in vitro* and *in vivo*, reducing tumor volume by 30% compared to control groups⁹².

In our approach, we have been developing PLGA nanoparticles as a sustained nonviral gene expression vector and demonstrated their efficacy with tumor suppressor p53 gene in different tumor models^{93,94}. It has been known that tumors with p53 mutation are associated with more aggressive disease, as well as increased resistance to chemotherapy and radiotherapy. Targeting gene- or drug-loaded nanoparticles (NPs) to tumors and ensuring their intratumoral retention after systemic administration remain key challenges to improving the efficacy of NP-based therapeutics. In this regard, we have been investigating a novel targeting approach that exploits changes in lipid metabolism and cell membrane biophysics that occur during malignancy. Recently, we have demonstrated that surface modified NPs which show greater biophysical interactions with the lipids of cancer cells than with the normal cell lipids show increased NP uptake by cancer cells *in vitro*, enhanced tumor accumulation *in vivo*, and improved efficacy of gene therapy⁹⁵. In another study, we are exploring biophysical interactions with the lipids of drug resistant cells in order to develop NPs that can overcome drug resistance^{96,97}. Our studies suggest a role of NP-lipid biophysical interactions in developing NP-based therapeutics. Thus, characterization of the biophysical interactions between NPs with different surface characteristics and lipid membranes of tumors may be a promising approach for screening and developing targeted delivery systems⁹⁸.

Another target of research involves vascular endothelium and limiting angiogenesis in tumors. Integrin α_3 , an internalization receptor for a number of viruses, has been shown to be expressed on angiogenic endothelium in malignant or diseased tissues⁹⁹. Murphy et al designed α_3 -targeted NPs capable of delivering pharmacological agents to the α_3 -expressing tumor vasculature¹⁰⁰. A metastatic RCC mouse model was used and doxorubicin was loaded into NPs. The results showed improvement in incidence of metastatic disease and total metastatic burden as compared to drug alone as well as yielding limited side effects¹⁰⁰.

Tetraiodothyroacetic acid (Tetrac), a thyroid hormone antagonist, has previously demonstrated antiproliferation effect on cells¹⁰¹. Tetrac acts as an antagonist at the integrin receptor on the cell surface and suppresses angiogenesis along with its binding to thyroid hormone receptor within the cell. To determine the mechanism of tumor growth suppression of Tetrac, PLGA NPs encapsulating Tetrac were created with a size of 200 nm, prohibiting uptake into cells¹⁰². In a mouse model of RCC, it was shown that both tetrac and tetrac NP have similar effects on inhibition of cancer cell proliferation and angiogenesis supporting the notion that tetrac acts on the integrin α_3 receptor on the plasma membrane¹⁰². Thus, there may be an application for NP encapsulated Tetrac where the effects of thyroid hormone receptor would be avoided.

Local treatment

Localized RCC can be cured with surgical excision; however survival decreases dramatically with lymph node involvement. There exists conflicting evidence regarding the benefits of lymph node dissection (LND) at the time of radical nephrectomy for clinically localized RCC^{103–106}. Potentially, the utility of LND would be realized if the correct patients were selected with more sophisticated pre-operative imaging identifying lymph node involvement. Current imaging with CT, MRI, and PET have limited capabilities for distinguishing metastatic lymph node involvement, specifically smaller sized nodes¹⁰⁶. Lymphotropic NP-enhanced MRI has been shown to be effective and accurate at distinguishing benign from malignant lymph nodes in prostate cancer¹⁰⁷. In 9 patients with imaging suggesting localized RCC, lymphotropic NP-enhanced MRI was performed with and without magnetic NPs called ferumoxtran-10 (Combidex, AMAG Pharmaceuticals, Inc.) followed by radical nephrectomy and LND¹⁰⁸. Although small in patient size and number of metastatic events, the study showed high sensitivity (100%) and specificity (95.7%) for distinguishing metastatic lymph nodes with magnetic NP-enhanced MRI.

Radiofrequency ablation (RFA) for treatment of small renal masses has become widely accepted due to its minimally invasive nature and ability to spare nephrons. However, tumors amenable to RFA are restricted by size and proximity to hilar structures or adjacent organs. During RFA, tumor is destroyed most completely at the center of the inner zone and from there circumferentially cell death dissipates. RFA efficiency would increase if the region of total cell death could be increased without expanding the total area of thermal injury. Tumor necrosis factor- α (TNF- α) targets tumor cells and vasculature, but has dose-limiting toxicities when administered systemically¹⁰⁹. Gold NPs loaded with TNF- α have been previously shown to accumulate within tumor interstitium with reduced systemic toxicity¹¹⁰. From these studies, it was then shown that gold coated TNF- α NPs were able to sensitize the tumor so that the region of cell death when injected prior to RFA was increased by 23%¹⁰⁹.

Another minimally invasive approach to treating RCC involves magnetic thermoablation, or the application of energy on targeted tissue to achieve necrosis. Iron oxide NPs are exposed to an alternating electromagnetic field producing heat¹¹¹. Using these NPs as a ferrofluid, a rabbit model for RCC was created and the ferrofluid injected into the tumor under CT-

guidance¹¹². The animal was exposed to an alternating electromagnetic field for 15 minutes and then the organs harvested for assessment. They found that percutaneous injection of the fluid was technically feasible, although there existed variability in how much tumor tissue showed histologic evidence of treatment in each animal as there remained areas free of necrosis¹¹². A more complete method of delivery of the ferrofluid to the tumor is needed, but this study does show the feasibility as well as the ability to monitor the effects of ferrofluid thermablation by CT scan.

Nephrotoxicity of Nanoparticles

Tissue distribution and toxicity of IV or GI administered biological NPs are of interest as the field of nanomedicine grows. Toxicity to the kidneys is often a limit of drug delivery, which has not been extensively investigated with NPs in particular. SiO₂ NPs have been investigated in a number of biomedical systems. Wang et al studied the toxicity of SiO₂ NPs *in vitro* with an embryonic kidney cell line and showed that cell viability decreased with an increase in dose and increase in time exposed¹¹³. Microscopically, cells exhibited features of apoptosis. NPs of 20 nm were more toxic than 50 nm NPs, likely owing to how the renal filtration handles particles of different sizes. Patra et al investigated toxicity of gold NPs on 3 different cell lines *in vitro*, one of which was baby hamster kidney¹¹⁴. This cell line showed no effect on cell morphology or cell viability after treatment with the gold NPs at various doses (versus substantial morphologic changes and decreased survival in a liver cell line). Toxicity of NPs used for enhanced imaging has been studied *in vivo*. Sadaf et al examined quantum dot NPs with silica coating administer intravenously to mice and found no increased in measure serum urea nitrogen or creatinine levels as well as no morphologic changes on histochemistry examination¹¹⁵. Sodium-oleate-coated USPIO have been studied *in vivo* in a rat model administered as a single dose at varying concentrations and followed for 1 month. There was no change in renal function or cellular morphology¹¹⁶. While these studies highlight some of the properties of NPs and how they may affect the kidney, there exist no *in vivo* human studies that particularly investigate the toxicology profiles of these biological NPs.

Summary

This review highlights areas of active clinical practice with NPs in the fields of nephrology and urology. NPs have been deployed in renal imaging techniques and delivery of iron therapy with Ferumoxytol for CKD or ESRD patients who lack appropriate erythropoietin production. There exist active areas of research with NPs in animal models. Hypertensive and atherosclerotic rodents have shown major improvements in disease state with brief treatment periods. NPs are able to sensitize renal tumors to minimal invasive techniques such as RFA for improved cell necrosis. Magnetic assisted hemodialysis with toxin scavenging NPs shows promise *in vitro* of improved solute clearance in shorter dialysis sessions, which would greatly improve the quality of life of these patients.

The strategies and advancements reported here are merely a sliver of the possibilities that NPs could contribute to advancing the treatment of kidney diseases. Challenges exist regarding translating the work from the bench to bedside, limiting clearance of the NPs by the kidney while targeting treatment to the appropriate tissue or area of disease, and demonstrating the biocompatibility of different nanostructures.

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Figure 1.
The properties of NPs are able to be modified by size, shape, charge, hydrophobicity, and with targeting agents such as amino acids, proteins or ligands.

Figure 2.
The enhanced permeability and retention effect of tumor vasculature and lymphatics. Leaky blood vessel endothelium allows escape of small particles such as NPs into the surrounding tumor. Poorly organized lymphatic channels increased retention of the NPs at the target tumor.

Figure 3.
Schematic for different applications of Nanotechnology in kidney diseases.

Table 1

Characteristics of NPs with renal targeting

	Characteristics	Renal Target
Size	80–100 nm gold core NP	Mesangium
	4–6 nm iron oxide core NP	Cortex, nephritis
Conjugation	MHC-II antibody	Medulla
	Anti-CDIIb antibody	Unilateral obstruction
	Integrin 3	Tumor vasculature
Encapsulation	PLGA coated CoQ10, superoxide scavenger	Vascular endothelium
	Dendrimer	Medulla during ischemia
	Dextran coated iron oxide	Cortex during allograft rejection
	Peg coated nucleic acids	Cell nucleus, gene therapy
	TNF-	Tumor interstitium