



Nanotechnology Enters the Renal Cancer Drug Delivery Arena: A Review



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Abstract

Unique pharmacokinetics, minimal renal filtration, controllable size and shape, high surface-to-volume ratios, easy functionalization to attach ligands, therapeutic agents and navigating molecules so that they can be internalized are the properties of nanoparticles that have been used to deliver drugs to various cancer cells. Entry of nanotechnology for targeted drug delivery to renal cancer is in its infancy. This review apprehends the arsenal of different types of nanocarriers available that can be used for selective tumor targeting, and challenges in renal cancer treatment. Nanocarriers are much smaller than cancer cells therefore can be taken-up through leaky blood vessels and interact with targeted tumor-specific proteins both on the surface and inside cancer cells. Use of nanoparticles to thermally ablate kidney cancer is also touched upon. This review suggests that in future, owing to the efficacy of these novel agents, the therapy of renal cancer appears promising.

Keywords: Renal Cancer; Tumor; Nanotechnology; Drug deliver; Multi-Target Inhibitors.

Abbreviations: RCC: Renal Cell Carcinoma; TCC: Transitional Cell Carcinoma; SPIONs: Super-Paramagnetic Iron Nanoparticles; MITs: Multi-Target Inhibitors; SDI: Single-Drug Inhibitor; MDI: multi-drug inhibitors; VEGF: Vascular Endothelial Cell Growth Factor; EPR: Enhanced Permeability and Retention; BHD: Birt-Hogg-Dube; RES: Reticulo-Endothelial System; SLN: Solid Lipid Nanoparticles; CNTs: Carbon Nano-tubes; MWCNT: Multi walled CNT; SWCNT: Single Wall CNT; QD: Quantum Dot; NIR: Near Infra-Red Region; Dox: Doxorubicin; VNPs: Viral Nano Particles; CPMV: Cowpea Mosaic Virus; IFN α : Interferon alfa; IL-2: interleukin-2

Introduction

Renal (kidney) system is a filter to purify the blood. Renal cortical tumor could be malignant, indolent or benign [1].

Types of Renal Cancer

- i. Renal Cell Carcinoma(RCC): That develops in the proximal renal tubules[2] having four major histological cell types i.e. Clear-cell, Papillary, Chromophobe and Collecting-duct [3].
- ii. Transitional Cell Carcinoma(TCC): Begins in the lining of the transitional cells of renal pelvis that line the ureters and bladder [4].
- iii. Renal Sarcoma develops in the thin layer of blood vessel or connective tissue surrounding the kidney [5].
- iv. Wilms Tumor (Nephroblastoma) forms in the kidney tissues that make urine [6].
- v. Primary Renal Lymphoma is enlarged lymphadenopathy [7].
- vi. Benign Kidney Tumor: Grows but do not metastasize.

Proteomics/metabolomics, mutational searches, gene expression profiling, and pathological/clinical studies have characterized different signalling pathways and many oncogenes and tumor suppressor genes associated with renal tumors, including those involved in tumorigenesis, progression and outcome of the cancer [8].

Major signalling pathways involved in RCC are:

- (i) von Hippel-Lindau Gene Inactivation [9]
- (ii) mTOR Pathway [10]
- (iii) NF- κ B Pathway [11]
- (iv) NOx Pathway [12]
- (v) Tyrosine Kinase Pathway [13]
- (vi) HSP70 Pathway [14]
- (vii) Mitogen-Activated Protein Kinase Pathway [15].

Conventional Therapeutic approaches to RCC (Surgery, Chemotherapy, Immunomodulatory therapy, Adjuvant therapy,

Radiation therapy etc.) are guided by the stage or degree of tumor dissemination. Medical therapies are generally offered for locally advanced or metastatic renal-cell carcinoma in patients with the clear-cell type [3]. As response rates are low, the need to identify new therapeutic agents is great [16]. Other therapies as stem cell transplantation, targeting specific antigen e.g. G250 renal cancer antigen, which has been identified as CA9 [17] and combination of therapies targeting specific growth factors [18] is now being researched. RCC is highly resistant to chemotherapy. Generally, interleukin-2 or interferon alfa is used as first-line treatment of metastatic disease, but response to these cytokines is low. There are no alternative treatments for RCC that is resistant to cytokines; though some trials of treatment with an anti-angiogenic agent are being done [19].

Why Nanotechnology

Conventional drug delivery methods, harms both cancer and healthy cells, creating the need for targeted active and passive drug delivery.

The nanoparticles (1- 100 nm) have altered physicochemical properties hence. exhibit altered interactions with cells and tissue. Nanoparticles can be used as drug delivery vehicle for targeted as well as controlled (timed release or single dose administration) drug release either by. Moreover, antibodies, nucleic acid, protein and peptides, needed for targeted drug delivery can also be carried by nanoparticles to the site of action. This avoids over dosing, side effects and harming the healthy cells [20]. Molecules can be attached either on the surface or encapsulated within. Encapsulation is of great advantage for suspension of insoluble drugs [21] and protection from degradation in the body prior to reaching its site [22]. Many therapeutic molecules used for kidney have rather poor pharmacokinetics [23], many small molecules are filtered and cleared from the kidney before they can have therapeutic effect or even cleared by the hepatic activity thus giving even less exposure to kidney.

Nano-vehicles has to be biocompatible, water soluble, pH specific, can protect premature drug delivery, has extended circulating life in the body, controlled interaction of drug with cellular environment and easily functionalize and disposable after the drug delivery. The pharmacokinetic profile of nanoparticles has been found to be unique, including minimal renal filtration. Nanoparticles have high surface to volume ratio, their surface can be modified by several functional groups so as to help in stabilizing and internalizing therapeutic agents. The drug distribution in tissues profile have exhibited increased differential uptake in the targeted cells than the healthy cells. Moreover, unique optical, electrical, magnetic and thermal properties of nanoparticles such as gold, silver, super-paramagnetic iron nanoparticles (SPIONs) are being used for treating cancer through photothermal killing of tumor cells [24].

Renal Cancer being a multifactorial disease needs multi-target inhibitors (MITs) to take care of complications like development of resistance. Both single-drug inhibitor (SDI) and multi-drug inhibitors (MDI) are being used. At present there is no cure of metastatic RCC, therefore very limited use of nanotechnology is available. Potential of nanotechnology to develop early diagnostic devices such as sensing, imaging and remote actuation that can be combined with therapy will be of dual advantage.

Nanoparticles Can Enter Cancer Cells Through Leaky Blood Vessels

Cancerous tumors faces hypoxia hence needs more oxygen and for the growth of dormant avascular nodule needs more nutrients. Hypoxia condition activates angiogenesis i.e. new uncontrolled and excessive growth of blood vessel that gives rise to leaky blood vessels, through up-regulation of angiogenic cytokines and Vascular Endothelial Cell Growth Factor (VEGF). Angiopoietin such as integrins; are released by the tumor and host cells near the tumor. Hence, angiogenesis inhibitors drugs to block the angiogenesis in kidney cancers as anti VEGF such as Axitinib, Bevacizumab, Everolimus, Pazopanib, Sorafenib, Sunitinib, Camptothecin etc are in use. Tumors tissue has leaky blood vessels and poor lymphatic drainage. If drug is delivered using Nano-carrier it will extravasate into the tumor via leaky vessels by the enhanced permeability and retention (EPR). The dysfunctional lymphatic drainage in tumor facilitates nanocarriers to accumulate in tumor tissue and release drugs into the vicinity of the tumor cells. Whereas, free drug delivered by conventional methods often diffuse non-specifically into all cells. Nanoparticles-based drug delivery enhances permeability and retention (EPR) effect thus accumulating more nanoparticles in tumor tissue than in normal tissues by easy transfer of nanoparticles through the leaky blood vessels, which interacts with targeted tumor specific proteins, both on the surface and inside the cancer cell.

Major barriers in extravasations (leakage) of nanoparticles into the tumors are renal filtration, transport from plasma into tumor interstitial fluid among endothelial cells lining vessels and distribution within tumor interstitial fluid.

Physiological and Biological Suitability of Nano constructs for Drug Delivery

The characteristics for ideal drug delivery system are response to biologically relevant stimuli, stability, low toxicity, passive and active targeting. Micelle a Nano construct in which core is used for storing the drug and the outer core is functionalized to modify its physicochemical characteristics to facilitate the drug delivery [25]. To prepare such nanoparticles polymers are also good option, which is achieved by heterogeneous polymerization of monomers [26]. For passive targeting characteristic features of tumors biology such as leaky

blood vessels and poor lymphatic drainage, are exploited to allow the accumulation of nanocarriers in tumor by EPR effect.

Targeted Drug Delivery to Renal Cancer

Before considering targeted drug delivery to renal cancer cells it is important to have a cursory glance at the types of Renal Cancer Cells (RCC). There are as many as 20 different types of kidney cancer cells. RCC originates from the tubular structures of the kidney and is classified into four major histological cell types: Clear cell, papillary, chromophobe and collecting duct [3].

Clear Cell

Approximately 70% of kidney cancers are made up of clear or very pale cells ranging from slow growing (grade 1) to fast growing (grade 4). These cells are responsive to immunotherapy and targeted therapy [27,28].

Papillary

It is the second most common subtype of renal cancer. ~10% renal cancers show presence of papillary cells (type 1 and type 2). This cancer forms finger-like projections (papillae) and are responsive to immunotherapy and targeted therapy [29]. No kidney cancer therapies have been developed to combat papillary renal cancer, though few are in development by the pharmaceutical companies [30].

Sarcomatoid Features Carcinoma

Disorganized clear cell, papillary and chromophobe, described by pathologists as “sarcomatoid” are indicative of very aggressive form of kidney cancer [31]. It accounts for approximately one in six cases of advanced kidney cancer.

Medullary/Collecting duct

An aggressive cancer closely related to TCC. It is common in black people and is highly associated with having the sickle cell trait [32,33].

Chromophobe

An uncommon cancer that accounts for ~5% of renal cancer that may form indolent tumors. These cancers cells are pale, like the clear cells, but are much larger [34,35].

Oncocytoma

A benign slow-growing tumor that rarely spread to different organs [36].

Angiomyolipoma

A benign tumor best treated with surgery, and rarely found in an aggressive form epithelioid, which could spread to nearby lymph nodes or organs. These tumors are made up of different types of connective tissues (blood vessels, smooth muscles, and fat) [37]. They occur sporadically, and risk of life threatening hemorrhage is the main clinical concern.

Pathogenesis of renal cancer is complex and diverse and is influenced by multiple factors, some of which are related are smoking, obesity, work place exposure, genetic and hereditary risk factor, gene mutation (inherited or acquired) and presence von Hippel-Lindau disease, Hereditary papillary renal cell carcinoma, Hereditary leiomyoma-renal cell carcinoma, Birt-Hogg-Dube (BHD) syndrome, Familial renal cancer, Hereditary renal oncocytoma, Family history of kidney cancer and high blood pressure [38].

In conventional therapeutic method drug is absorbed through the membrane, often more than required and delivered to healthy tissues also. Whereas drug loaded nanoparticles along with navigating molecule delivers drug to specific tissue and avoids interaction with healthy tissue thus protecting them and are effective at reduced dose leading to minimized side effects.

There are two approaches for targeted drug delivery - Passive Targeting and Active Targeting.

i. Passive Targeting

No navigating molecules are added to the drug loaded nanoparticles and they are directly delivered and accumulated in the tumor by the EPR effect. Passive targeting is done by extravasation of nanoparticles through increased permeability to tumor microenvironment, direct application and leaky tumor vasculature and EPR effect. Since EPR-effect is used as main criteria, therefore it is directly related to circulation time [39]. Liposome and polymer-protein conjugates are used for passive targeting. The surface of nanoparticles are coated with substances such as PEG to make it hydrophilic and the particles become hydrated, which makes this conjugate anti-phagocytic, thus the drug-loaded nanoparticles have prolonged stay in circulation. 10-100 nanometers are suitable and circulate for longer period [40].

ii. Active Targeting

Deciding a navigating molecule (antibody, folates/folic acid or vitamin) to be attached to the drug loaded nanoparticle; depends on the over expressed receptors on the membrane of cancer cells to which the drug will be targeted. Then it is easy to utilize cell-specific ligands that will allow for the nanoparticle to bind specifically to the cell that has the complimentary receptor and deliver the drug by endocytosis. Transferrin is a good cell specific ligand to be conjugated with nanoparticles to target tumor cells having transferrin-receptor mediated endocytosis [41].

Active Targeting can be achieved by (i) Carbohydrate-directed targeting, (ii) Receptor- and Antigen-directed targeting (iii) desired characteristics of Ligands and Antibodies (iv) Magneto-liposomes and (v) Peptide based drug targeting system [42]. A combination of both passive and active targeting using

nanoparticle has advantage over conventional drug delivery [43].

Overcoming Barriers Specific Biological Barriers: Penetrating Stroma

The biological barriers in the human body are epithelia, endothelia, vascular endothelium; endosome, vascular endothelium, membranes of the cell and nucleus, activated monocytes and macrophages of the reticulo-endothelial system (RES), enzymatic degradation; sequestration by the phagocytes of the RES; adverse oncotic and interstitial pressures in the tumor; tumor interstitium and molecular efflux pumps for the elimination of therapeutic agents. The sequential nature of barriers demands consideration for nano-vectors, surface modifications, therapeutic agents and penetration enhancers to be used for a multi-stage drug delivery strategy. The nanoparticles have to negotiate with all these barriers in order to attain a sufficient therapeutic index. In renal cancer there is a problem of restricting removal of drug and / or nanoparticles with filtration before they can exert their effect. In some situations, instead of delivering therapeutic agent to the cancer cells it is needed to be delivered to the other cell types within the tumor like macrophages or stromal tissue, which has been successfully done by polymeric nanoparticle to deliver siRNA to tumor-associated macrophages [44].

Need of Multi-Target Inhibitors (MTIs)

In multifactorial diseases complications that arise are development of resistance and toxicity due to non-specificity of drug delivery. Renal cancer being multi-factorial disease needs MTIs using either single-drug inhibitor (SDIs) or multi-drug inhibitors (MDI).

SDIs such as Kinase inhibitor simultaneously affect the multiple pathways, whereas MDIs inhibit multiple pathways because many combinatorial agents are used that act synergistically. Drugs for RCC that are in preclinical or clinical stage are Sorafenib, Sunitinib, Pazopanib and Cabozantinib. These drugs inhibit Vascular Endothelial Growth Factor Receptor; Platelet Derived Growth Factor Receptor and Mitogen Activated Protein pathway [45-47].

MTIs inhibit multiple signaling pathways thus has potential to cause systemic toxicity. Use of nanoparticles for targeted delivery of MTI ensures its accumulation in the tumor vasculature and reduces the systemic side effects. MDI uses synergistic drug combinations, which enhances the efficacy. Berenbaum [48] had suggested the use of combination agents as a solution for cancer therapy. Using nanotechnology, the ratio of different agents can be tailored to achieve optimal for different targets. Gowda et al. [49] have theoretically explained that if three inhibition agents are combined for MDI they cause 90% tumor inhibition, whereas separately they cause much less i.e. agent 1 causes 10%, agent 2 causes 20% and agent 3 causes 10%; in total only 40% inhibition.

Suitability of Nanoparticles for Targeted Drug Delivery

Use of nanotechnology for delivering drugs to renal cancer is still in its infancy. Kidneys filter blood through a structure known as the glomerular capillary wall. Nanoparticles <10 nm diameter faces first pass renal filtration, hence, size of nanoparticles is very important. Dreher et al. [50] have shown that particles >100 nm diameter can accumulate in the tumor tissue, while being passively targeted, which is entirely dependent on diffusion-mediated transport into the tumor. Stable nanoparticles that are in circulation for longer period, results in enhanced drug uptake by tumor and by avoiding reticuloendothelial system it minimizes the toxicity.

Nanospheres

(Figure 1a) can self-assemble, are biodegradable, their matrix is made of bovine serum albumin [51] or other amphiphilic copolymers [52], in which drug molecules are uniformly distributed. Nanospheres when used for delivering anti-angiostatin and endostatin (anti VEGF) [53,54] were found to be long circulating. Composition of the polymer matrix and its ability to imbibe fluids determines how rapidly the drug will be released [55]. These properties indicate that if tried Nanospheres may be suitable for delivering drugs to renal cancer tumor.

Nanocapsules

(Figure 1b) are composed of polymeric membranes and core of oil, which encompasses drugs [56] that can diffuse out under appropriate conditions, by responding to environmental, chemical, thermal or biological triggers [57-60]. Nano capsules are colloidal and synthesized by interfacial deposition of preformed polymers [61] (PLA, PLGA, PCL and PEG) [62-64]. It is suitable for the delivery of hydrophobic drugs. Lipid nanocapsules have been used for multi drug resistant cases in rat tumor [65]. Though not much work has been done on drug delivery to RCC using nanocapsules, but Hureau et al. [66] have suggested a novel hybrid protein-lipid polymer nanocapsule of 180nm as nontoxic drug for co-delivery of transcription factor p53 and lipophilic drug paclitaxel to induce HeLa cell apoptosis; this gives incentive to try using nanocapsules for delivering drugs to RCC.

Micelles

They are amphiphilic block of copolymers, that are biocompatible, biodegradable and self assemble in aqueous solution. They are aggregate of molecules in a colloidal solution, that can be Anionic (Sodium dodecyl Sulfate), Cationic (Cetylpyridinium bromide), Zwitterionic (lecithin) or Non-ionic (Polyoxyethylene Lauryl Ether). There are reverse and bilayer micelle (Figure 1c). Drugs entrapped in micelles have shown increased vascular permeability and impaired lymphatic drainage [67], causing EPR effect, suitable for passive targeting and can be used for controlled drug release [68]; thus, showing a potential for its use in RCC therapy. Suitability of micelle for

MTI drug delivery [21]; for concurrent delivery of two or more MTI modalities [69]; as stimulus-responsive targeted [58]; easy tailoring to optimize delivery to solid tumors [70] and delivery of poorly soluble drugs [71] have been observed.

Nano-Liposomes

They are spherical, concentric bilayered vesicles having phospholipid membrane (Figure 1d). The amphiphilic nature of liposomes, their ease of surface modification and a good biocompatibility make them an appealing solution for increasing the circulating half-life of proteins and peptides. The hydrophilic compounds remain encapsulated in the aqueous interior and hydrophobic compounds can escape encapsulation by diffusion through phospholipids membrane. Nano-liposomes can be designed to adhere to cellular membranes to transfer drugs following endocytosis. 100-200 nm nano-liposomes can rapidly

enter tumor through vasculature. In nano-liposomes at a time many different molecules can be attached to the surface. PEG linked nano-liposomes are highly stable and have been used to deliver drugs to Brain [72] and colorectal cancer [73] but not for renal cancer. Since renal cancer has multiple signaling pathway, many nano-liposomal formulations containing therapeutic agents, antisense-oligodeoxynucleotides, siRNA, DNA or radioactive particles that can target multiple signaling pathway are being used for cancer treatment [74] and it can be of potential use for renal cancer also.

Use of nano-liposomes to deliver iron-oxide nanoparticles [30] for photothermal therapy of tumors and conjugation of nanoparticles of gold with liposomes for photothermal therapy and multi-modal imaging [75] have also generated hopes for its use in renal cancer treatment.

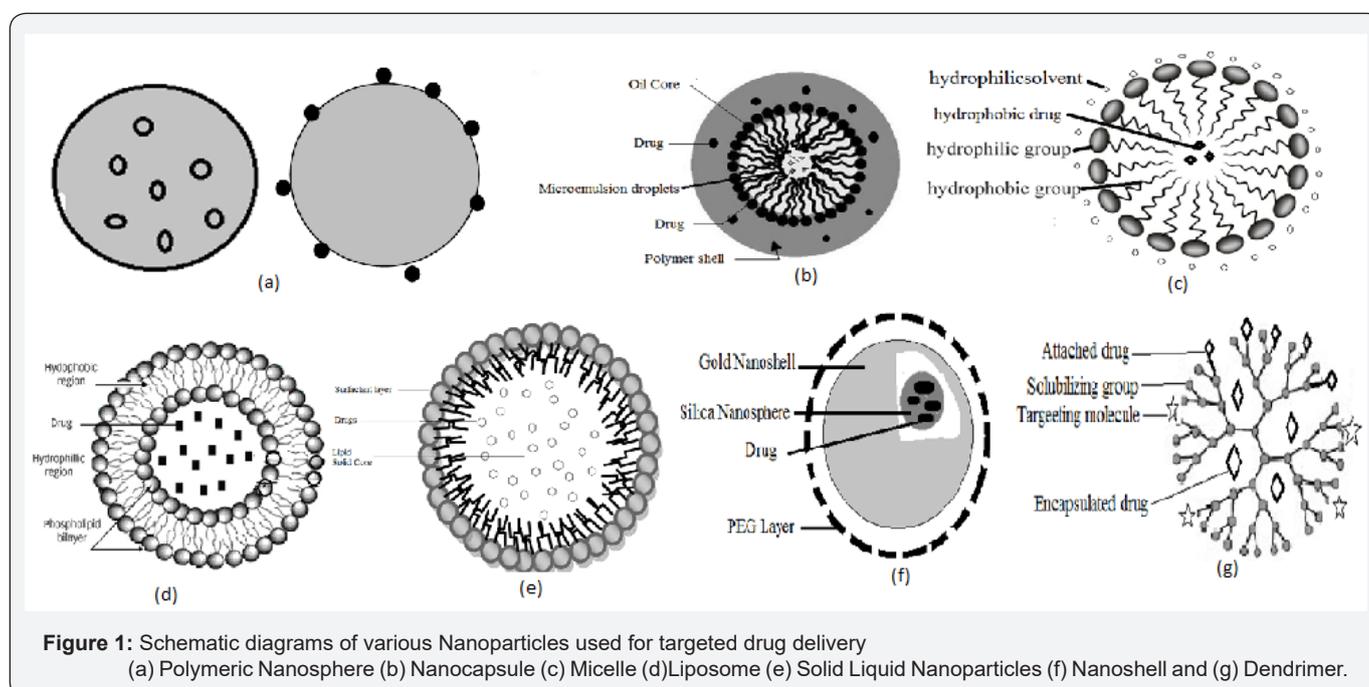


Figure 1: Schematic diagrams of various Nanoparticles used for targeted drug delivery (a) Polymeric Nanosphere (b) Nanocapsule (c) Micelle (d) Liposome (e) Solid Lipid Nanoparticles (f) Nanoshell and (g) Dendrimer.

Solid Lipid Nanoparticles (SLN)

They are colloidal, spherical, drug carrier system [76] having solid lipid core matrix that can solubilize lipophilic molecules (Figure 1e). Lipids used are triglycerides (tristearin), diglycerides (glycerol behenate), monoglycerides (glycerol monostearate), fatty acids (stearic acid), steroids (cholesterol) and waxes (cetyl-palmitate). SLN are easy to biodegrade, less toxic than polymer or ceramic nanoparticles. Surface tailoring of SLN to load drugs is easy. SLNs can ferry bioactive selectively and specifically to the tumor sites with the interception of minimal side effects. They have controllable pharmacokinetic parameters and can be engineered with three types of hydrophobic core designs: a homogenous matrix, a drug-enriched shell or a drug-enriched core. Zariwala [77] has shown use of SLN (lipid matrix composed of stearic acid) for oral iron delivery. Gaspar et al.

[78] have used SLN as transporter of therapeutic protein to lung epithelium. SLN can be an alternative to Liposomes and other polymeric nanoparticles. PEGylated SLNs has increased stability, bio-distribution and bio-availability of the conjugated drugs. Fundaro et al. [79] have demonstrated that PRG coated SLN carrying anticancer drug doxorubicin that reaches cancer cells in solid tumors more effectively than healthy tissues.

Nanoshells

They are spherical nanoparticle consisting of a dielectric core of silica covered by thin metallic shell (Figure 1f). Gold nanoparticles are preferred as outer layer of the shell because they are biocompatible and different types of molecules can be attached to them. Nanoshell can be injected safely. Phagocytes engulf the nanoshells through the cell membrane to form an internal phagosome. Nanoshell decorated with antigens that

are expressed in cancer cell or tumor microenvironment; preferentially concentrate in the cancer cell because of their size and have enhanced EPR capacity. When light energy or radio frequency is externally applied to the cells where nanoshells are located, they create intense heat that selectively kills the tumor cells. The nanoshells can act as theranostic agent as they can be simultaneously used for detection and drug therapy.

Dendrimers

They are spheroid/globular nanoscale macromolecular compounds that form branches around the core (Figure 1g), offering multiple attachment sites for drug, antibody etc. The solubility and reactivity of dendrimer is influenced by the nature of surface groups. Dendrimers terminated in hydrophilic groups are soluble in polar solvents; whereas, dendrimers having hydrophobic end groups are soluble in non-polar solvents. Dendrimer solutions have significantly lower viscosity than linear polymers. Cationic (surface) charges are more toxic but it also depend on the specific groups involved, e.g. primary amines are relatively more toxic than secondary or tertiary amines. Anionic dendrimers, bearing a carboxylate surface are not cytotoxic over a broad concentration range.

There are three sections of dendrimers (Figure 1g), the outer multivalent surface containing potential reactive sites; layers below the surface have branches and few internal cavities and inner core. Based on their chemical structure the types of dendrimers are:

- i. PAMAM Poly (amido-amine)suspended in methanol solutions.
- ii. PAMAMOS are radially layered poly(amidoamine-organosilicon), which are inverted unimolecular micelles consisting of hydrophilic, nucleophilic PAMAM interiors and hydrophobic organosilicon exteriors.
- iii. PPI-dendrimers "Poly (Propylene Imine) has primary amines as end groups and tertiary tris-propylene amines as interior.
- iv. Multilingual dendrimers have surface composed of multiple copies of particular functional group.
- v. Hybrid Dendrimers are Linear Polymers block or graft polymers of dendritic and linear polymers.
- vi. Amphiphilic dendrimers has two segregated sites of chain end, one half is electron donating and the other half is electron withdrawing.
- vii. Micellar dendrimers are unimolecular water soluble hyper branched polyphenylenes.
- viii. Multiple Antigen Peptide dendrimers are dendron-like molecular construct based on a polylysine skeleton.
- ix. Fréchet-Type is based on poly-benzyl ether hyper branched skeleton having carboxylic acid as surface groups,

serving as a good anchoring point for further surface functionalization, and as polar surface groups to increase the solubility of this hydrophobic dendrimer in polar solvents or aqueous media.

x. Tecto Dendrimers are composed of a core dendrimer, surrounded by dendrimers of several steps to perform a function necessary for a therapeutic nanodevices.

xi. Dendrimer based drug delivery system is already commercialized by Starpharma.

Ceramic-Nanoparticles

These are inorganic, heat-resistant, non-metallic solids made of both metallic and non-metallic compounds. Nano-ceramics are not brittle, they are dielectric, ferroelectric, piezoelectric, pyroelectric, ferromagnetic, magneto resistive, superconductive and electro-optical. They are fabricated from inorganic compounds of silica, titania etc. The silica based nano-ceramics are used for entrapping and releasing water insoluble drugs, it has potential of being used as drug carriers for photodynamic therapy [80] and used for bone repair. Not much near future application of Nanoceramics in cancer therapy is envisaged.

Carbon Nano-tubes (CNTs)

These are sheet of graphene rolled up into cylindrical form as Multi walled CNT (MWCNT) or Single Wall CNT (SWCNT). The diameter of SWCNT is usually 2 nm whereas diameter of MWCNT varies as per layers of multi-walls and ranges from 3 to 30 nm. The size and surface properties of CNTs can be manipulated to circumvent rapid clearance by phagocytic cells, allowing both passive and active drug targeting. Controlled and sustained drug release from CNT can be obtained at the target site, improving the therapeutic efficacy and reducing side effects. Drug loading capacity of CNT is relatively high and may be achieved without chemical reactions by attaching drug directly to the dangling bonds present on the surface or inserting drug in CNT lumen (Figure 2a). CNT is chemically inert but use of CNT poses question regarding their biocompatibility and efficiency as a drug carrier. Functionalization of CNT has been tried to solve this problem by conjugating bioactive peptides, proteins, nucleic acids etc.[81]. Functionalized CNT displays low toxicity and are not immunogenic. Parihar et al.[82] have used functionalized CNT for the delivery of doxorubicin *in vitro*. CNT-based thermal tumor ablation therapies are being developed [83] by creating supra-physiologic temperature to kill malignant tissue [84] by denaturing the proteins and membrane lysis [85].

CNT has shown the potential for kidney cancer therapy. Joint efforts of Wake Forest University School of Medicine, the Wake Forest University Centre for Nanotechnology and Molecular Materials, Rice University and Virginia Tech, have shown that 80% of kidney tumors in mice was killed by injecting MWCNT into the tumors and heating them with a quick, 30-second zap of a laser. As compared to SWCNT, MWCNTs was found to be more effective at producing heat.

Usability of CNT for renal cancer therapy can be judged by the fact that chemical functionalization of CNTs influences the blood clearance profile via renal or biliary pathway [86]. CNTs of up to 25-30 nm diameters and upto 500 nm length can exit the blood stream and be excreted in urine [87]. Kostarelos et al. [88] have confirmed functionalization of CNT with hydrophilic groups aids in rapid renal clearance and low tissue retention. Shorter CNTs exhibit greater renal clearance than longer CNTs [89-91].

Wang et al. [22] have shown effective trans-membrane delivery of doxorubicin by endocytosis, using PEGylated oxidized mesoporous carbon nanospheres of 90 nm that was hydrophilic, stable, biocompatible, has high drug loading efficiency, could release drug under neutral pH and has prolonged circulation in the blood. The endocytosis, cytotoxicity, and anticancer effect *in vitro* and *in vivo* of the drug-loaded nanoparticles were also evaluated. It efficiently inhibited the growth of cancer cells both *in vitro* and *in vivo* and exhibited significant anti-metastasis effect in advanced stage of malignant cancer, improving the survival time of tumor-bearing mice. Thus, suggesting CNTs to be a promising anticancer drug delivery vehicle for renal cancer therapy.

Quantum Dot (QD)

Most of the QDs (CdSe, CdTe etc.) are highly cytotoxic. Capping of quantum dots with ZnS has been shown to augment stability and enhance luminescence with superior quantum yields at room temperature, however their suitability as drug delivery vehicle is still questionable.

Carbon quantum dots (CD) of 2-10nm [92] are being researched in medicine and theranostics due to its water solubility, small size, low toxicity, good biocompatibility, high photostability against photobleaching and blinking, broad excitation spectra, narrow and tunable emission spectra, synthesis from non-toxic precursors and above all having excellent Photoluminescent property in near infra-red region (NIR) which can be used for photothermal therapy also. A variety of carbon precursors such as graphene sheets, sucrose, amino acids, chitosan, carbon rich [93] and different surface passivation agents such as glutathione, PLGA, PEG have been used for the synthesis of carbon dots [94]. CD has been used for attaching and delivering antibiotics [95]. The anti-cancer drug doxorubicin (Dox) attachment capacity of Bovine Serum Albumin protected CD, using folic acid as navigational molecule has also been explored [96]. Internalization of CDs specifically by HeLa cell was noted that followed First Order model release at pH 7.2. Dox. CD exhibited higher killing of HeLa cells and less cytotoxicity to normal cell than free Dox. CD has shown a synergistic conjugation with gold nano rod for anchoring DOX via covalent and non-covalent pH sensitive chemical bonds [97]. This complex had 94% drug loading capacity under physiological conditions and showed a rapid release of Dox under NIR (808 nm) radiation, proving that it can be used for thermo-chemotherapy.

Metal and Inorganic Nanoparticles

They are composed of inorganic compounds such as silica or alumina metals, metal oxides and metal sulfides creating a myriad of nanostructures with varying size, shape, and porosity. It is relatively easy to modify the surfaces of these particles with unique functionalities via variety of chemical transformations. Inorganic nanoparticles are relatively stable over broad ranges of temperature and pH, yet their lack of biodegradation and slow dissolution raises safety questions, especially for long term administration. Metal nanoparticles have potential to produce monodispersity. Metallic nanoshells of 100 – 200 nm are used for imaging and therapy. Gold nanocages composed of gold nanorods, gold nanoparticles; iron oxide nanoparticles are examples of metallic nanoparticles and are used for diagnosis and thermo-ablative therapy. However, unlike polymeric nanostructures they are not biodegradable; this may cause accumulation in the body. Toxicity of nanoparticles can be reduced they can be excreted from the body by renal filtration by designing solubilizing organic coating which are biologically compatible with renal clearing. But the problem is that organic coatings often result in increase of the final hydrodynamic diameter.

Proteins and Antibodies

Glomerular proteins (LMWP) having MW < 30,000 Da, such as lysozymes (MW 14 kDa) are being tried as they selectively accumulate in the kidneys and are biologically active in the circulatory system. LMWPs can be filtered at the glomerulus and reabsorbed in the renal tubules, they are non-immunogenic, biodegradable [98]. LMWP has many functional sites for linking drugs [99].

Chitosan is a natural copolymer of glucosamine and N-acetylglucosamine. Acetylated low MW chitosan has been used for kidney-targeted drug delivery because it is biocompatible and biodegradable [20,100]. Using PVD (Poly (Vinylpyrrolidone-co-Dimethyl)); effect of MW and charge on its distribution in kidney [101] has been investigated; PVD of 6–8 kDa MW produced 80% renal targeting and good therapeutic effect. Peptides are also proposed as a targeting moiety for drug delivery chemotherapeutics. FITC-labelled G3-C12 peptide exhibited selective accumulation in mouse kidneys soon after injection.

Accumulation of actinomycin D-loaded isobutyl acrylate nanoparticles, an anti-inflammatory drug, in glomerular mesangial cells of rats have been reported [102]; where a nanoparticle-based therapeutics for targeting diseases that involve the kidney mesangium is constructed. It is Choi et al. [103] found that 75±25 nm diameter nanoparticles could be targeted to the kidney mesangium [18].

Attachment of Antibodies (Monoclonal Antibodies) to the surface of nanoparticles leads to targeting antigens present on the cancer cell membrane. So far unconjugated antibodies have been found to exert anti-tumor effect on many different types

of cancer such as lymphomas, breast cancers, non-Hodgkin's lymphomas, colorectal cancers and chronic lymphocytic leukemia [104,105]. The specificity of antibodies does active targeting of a variety of tumor types and distinguishes between healthy and cancerous cells. However, there are certain limitations in use of antibody-based cancer therapy such as process is complex, rather expensive, non-uniform uptake in tumor [105], lack of tumor penetration due to increase in size of nanoparticle caused by hydrodynamic radius of antibodies (~20nm) and an uneven distribution of antigens [105,106].

Viral Nano Particles (VNPs)

(Figure 2b) are emptied virus cells (empty of RNA) that can carry drugs to cancer cells. Usually plant viruses are chosen [107] because they are not pathogenic to human, biodegradable,

biocompatible, monodispersion, are easy to produce in large quantities, can self-assemble around a nanoparticle *in vitro*, hold approximately 10 cubic nanometers of particles [108]. Outer capsids of virus composed of protein building blocks can be chemically and genetically engineered with targeting ligands and therapeutic molecule. Drugs can be easily attached to the surface of VNP, this helps viral cells to bond to cancer cells only. Often positively charged nanoparticle systems e.g. dendrimers and polymers, induces toxic effect by damaging membrane structure [109,110], but positively charged VNP show enhanced tumor transport property and longer retention time in mammalian cells [111]. VNP can be engineered to stimulate immune response to their cognate virus [112]. Moreover, VNPs have been shown to be well tolerated by mammalian cells *in vitro*.

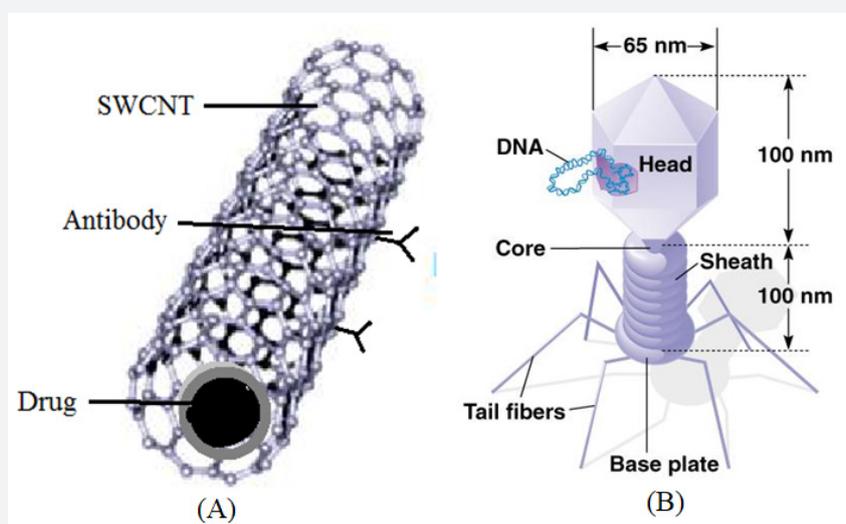


Figure 2: Schematic diagram of (A) CNT for drug delivery (B) A virus that can be used as cage for drug delivery (65 nm is capsids head).

Cowpea mosaic virus (CPMV) conjugated with iron oxide and using magnet from outside was tried to draw the nanoparticles to the cancer cells [113]. According to Franzen & Lommel [108] VNP connected with iron oxide has higher chance of being toxic to human cells. Other disadvantages of using VNP are that viruses are composed of protein that may attack human immune system. When CPMV VNP coated with polymers to mask the protein, was orally administered to mice, no evidence of toxicity in mice was found [114]. Orally administered CPMV accumulated in convoluted tubules of the kidney and in draining lymph nodes [115], suggesting its possible use in renal cancer therapy.

Grasso et al. [113] have successfully employed Tomato bushy stunt virus from *Nicotiana benthamiana* for drug loading and their retention in inner cavity. Other viruses from insects and animals have also been used to engineer VNP. Canine parvovirus responded to transferrin release in human body which is over expressed in tumor cells [114]. Coating VNP with integrin facilitated this process. An imaging agent can also be attached to it to facilitate in locating the tumor [116-118].

Nanotechnology for Targeted Drug Delivery to Renal Cancer

Surgery is main cure for treatment of renal cancer in early stage. However, recurrence after surgery or developing metastasis remains a big concern. Since RCC is a highly vascular disease, is resistant to chemotherapy, there are trials to explore immunotherapy. Cytokines, Interferon alfa (IFN α) and interleukin-2 (IL-2) treatment have been tried for metastatic RCC, but with very limited success [119,120]. Medicines such as Bisphosphonate and VEGF-targeted drug for the treatment of RCC metastasis are Cabozantinib [35], Sorafanib [33] are in use. Major considerations and strategies that are being employed to develop kidney-targeted drug delivery systems using nanotechnology, are to improve drug efficacy along with safety, assessment of types of nano-carriers, renal targeting conjugates, overcoming biological barriers and accessing the drugs to the cancer sites. Nanoparticles exhibit unique pharmacokinetics and minimal renal filtration. Passive targeting administration of

drugs can be difficult to access kidney tumor and it may involve injections or surgical procedures.

Kidney-targeted drug-delivery is focused on pharmacokinetic and pharmacodynamic studies in pathological conditions involving severe reductions in glomerular filtration. New nano-carriers are being constructed to target drugs to the glomerulus, mesangial cells and media fibroblasts. The cell surface receptor for folate is over expressed on the surface of kidney cancers/malignancies. Folate-conjugated PEGylated cyanoacrylate nanoparticles have shown higher affinity for the folate receptor than free folate [121-123] so they are going to be one of the most sought after drug delivery system to renal cancer. Both PEGylated and Non-PEG, 85- 100 nm Nano-Liposomes loaded with Lurtotecan and Annamycin are also being tried for RCC [71].

Torti [124] has shown some hope in treating tumor cancer by injecting CNTs in mice kidney tumor and then heating them with a laser for only 30 seconds, which killed 80% of kidney tumor. Mice that received (i) no treatment for tumors, (ii) CNTs only or (iii) only laser treatment; died within 30 days. Whereas mice injected with MWCNTs followed by 30-second laser treatment lived longer. Kidney tumors completely disappeared in 80% mice when highest quantity of MWCNTs was injected into the kidney tumors, these mice continued to live kidney tumor-free during nine months of study.

According to Torti "Multi-walled nanotubes (MWCNTs) are more effective at producing heat than other investigational nanomaterials," The speculations are that CNTs can be employed as drug delivery vehicle to deliver therapeutics to cellular level. However, prior to testing CNT in humans, studies need to be done to test the toxicity and safety if MWCNTs. Some considerations that should not be over looked are to minimize the accumulation of any non-biodegradable polymer or any other nanoparticle (used in drug delivery) having over the renal threshold size 31; and preventing the nanoparticles to cross the BBB.

Another issue that has been raised is can nanotechnology help in treating metastatic cancer that has cells of very small size, high multiplicity and are dispersed to diverse organ environments. For this the hope for very near future is only timely diagnosis. Delivering drugs to diverse organs, due to multifactorial causes of the cancer may take a lot of research to achieve.

Conclusion

Nanotherapy of renal cancer is still in its infancy. Occurrences of many different types of renal cancer, multifactorial nature of cancer and renal clearances are major hurdles. Suitability of different types of nanoparticles as drug carriers is discussed. CNTs have already been successfully used for hyperthermia treatment as well as drug delivery vehicle for renal cancer. Some considerations that should not be over looked are to minimize the accumulation of any non-biodegradable polymer or any other nanoparticle (used in drug delivery) having over the renal

threshold size 31; and preventing the nanoparticles to cross the BBB.

Another issue that has been raised is can nanotechnology help in treating metastatic cancer that has cells of very small size, high multiplicity and are dispersed to diverse organ environments. For this the hope for very near future is only timely diagnosis. Delivering drugs to diverse organs, due to multifactorial causes of the cancer may take a lot of research to achieve.

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