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THE IMPACT OF NANOTECHNOLOGY IN ACHIEVING SITE-SPECIFIC DRUG IMPACT OF NANOTECHNOLOGY AGAINST CANCER: AN EVALUATION OF SITE-SPECIFIC DELIVERY OF NANOMATERIALS FOR CANCER CELL TARGETING

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ABSTRACT

Nanotechnology is serving as an alternative way to overcome several limitations of conventional anti-cancer therapy in recent times. Among various nanosystems intended to annihilate cancer cells, just a predetermined number of them have undergone clinical trials. It is expected that progress in the development of nanotechnology-based anti-cancer drugs will give present day, individualized cancer therapies guaranteeing low morbidity and mortality. One significant aspect of cancer therapy is the site-specificity of the nanodrugs. There has been several attempts to design drugs in a way which enhances the drug's targeting potential while keeping the side effects very low. This review paper seeks to discuss nanotechnology for targeted drug delivery systems addressing challenges facing the fight against cancer therapy. We also offer a general summary of the advantages and challenges with general classes of drug delivery systems. Herein, we will further explore the novel strategies for targeted drug delivery and the advantages of using nanotechnology-based delivery techniques for cancer therapy and diagnosis. A discussion on ligands, receptors and advanced drug targeting will be presented in this review. Overall, this paper aims to provide a concise source of literature for drug delivery researchers.

KEYWORDS: Conventional anti-cancer therapy, individualized cancer therapies, site-specificity, targeted drug delivery.

INTRODUCTION

Cancer is one of the main sources of mortality in the world due to genetics and awful lifestyles such as exorbitant liquor intake and cigarette smoking, among others.[1,2] In recent years, various novel anti-cancer drugs, having pharmacological action including apoptosis, dysfunction in cell cycle, gene transcription and inhibition of angiogenesis process have been developed.[3] Nonetheless, tumor treatment continues to rely on joint technique of surgical mediation, radiation or chemotherapy. These techniques are still accompanied with a lot of difficulties in that anti-cancer drugs are toxic; they have poor selectivity, probability of cancer recurrence and the induction of drug-resistant cancer. In any case, research has demonstrated that these impediments can be overcome by utilizing new nanotechnology-based techniques.[4,5]

Various nano-materials comprising of engineered biodegradable polymers, such as chitosan (CS), polycaprolactone (PCL) or polylactic-co-glycolic acid (PLGA), lipids (liposomes, nanoniosomes, solid-lipid nanoparticles), mesoporous silica nanoparticles (MSNs), micelles, quantum spots (QDs), carbon nanotubes (CNTs) and iron oxide attractive nanoparticles (MNPs) have been employed for drug delivery.[6-12] Liposomes are self-assembled nano-or microparticles or colloidal carriers that form when certain lipids are hydrated in aqueous media. To enhance liposomal properties and increase the half-life, surface adjustment has been made with poly(ethylene glycol) and different agents so as to disallow their rapid clearance from circulation by cells of the mononuclear phagocyte system (MPS) to create long-circulating liposomes. Of late, multifunctional liposomes have been intended to specifically target cells or tissues of interest utilizing antibodies, aptamers, or different ligands as targeting agents.[13,14] On the other hand, polymeric nanoparticles are characterized as sub-micron-sized colloidal systems (1-1000nm) that can be created from an assortment of natural or synthetic polymers (biodegradable or non-biodegradable) of different composition. Leverage of utilizing polymeric nanoparticles is the improvement of novel methodologies to give different functionalities to the nanoparticle for targeted delivery.[15,16] Another relevant nano-based drug delivery agent is known as Quantum Dot (QD). QDs are small nanoparticles with typical diameters of a couple of nanometers (regularly <10 nm) which comprise of II–VI or sometimes III– V semiconductors in a core– shell structure. They demonstrate positive optical properties and a good resistance towards photobleaching which are exploited for biomedical imaging. Although their real application lies in the field of imaging, they are widely utilized for transfection due to their nature and size.[17] Carbon nanotubes have also

been portrayed as enlongated tubular nanostructures of graphene sheets with extraordinary physical, mechanical, and chemical properties.[18,19] Two distinct sorts are known: single walled carbon nanotubes (SWCNTs) and multi-walled carbon nanotubes (MWCNTs), with widths of a couple of nanometers and lengths up to 1 mm.[20] Their trademark property is their high proportion of length to breadth. They have been used as productive biosensors, as substrates for coordinated cell growth, as supports for the adhesion of liposaccharides to impersonate the cell membrane, for transfection, and for controlled drug release.[20] **Table1** summarizes the nano-carriers usually combined with targeting agents for drug delivery, their qualities and shortcomings.

It is obvious that advances in nanotechnology have contributed essentially to the improvement of novel nano-scale carriers in the field of medication delivery.[21-25] These nanoparticles are of fitting sizes (10-150 nm) capable of infiltrating vessels and gathering in specific tissues (e.g., tumors) and furthermore for their surfaces to be functionalized with particular ligands for targeting effects, giving a promising stage for drug delivery with improved therapeutic efficacy. To upgrade the viability of chemotherapeutics and diminish their side effects, different nano-particle(NP)- based medication delivery methodologies have been broadly studied.[26-30] Targeting of NP-based chemotherapeutics to tumors depends to a great extent on the improved permeability and retention (EPR) impact and the execution of NP surfaces with germane ligands which empower NPs to explicitly bind with disease cells. Current DDS ordinarily utilize vehicles to convey therapeutics keeping in mind the end goal to enhance the drug solubility, lessen toxicity, improve the half-life, restrict bio-distribution, achieve specific targeting, control drug release, and reduce immunogenicity. A perfect drug delivery vehicle ought to be biocompatible, biodegradable, simple to alter, and targeted towards a particular illnesses. An extensive variety of vehicles have been utilized as controlled DDS, e.g., liposomes[31], nanoparticles (NPs)[32], micelles[33], hydrogels[34,35], fibers[36,37], and films.[38] Concretely, nano- and micromaterials embellished with targeting ligands or molecules, such as peptides, antibodies, aptamers, and proteins, that are specific to the receptors expressed or overexpressed on aberrant cells and their circumventing microenvironments have been widely studied in targeted drug delivery.[39,40]

Lamentably, very few of these nanomedicines have shown clinical efficacy due to consequential challenges associated with the trafficking and targeting in vivo. Drug targeting strategies can be classified as either passive or active. Passive targeting is typically dependent

on enhanced permeability and the retention (EPR) effect caused by leaky vasculature and poor lymphatic drainage. The EPR effect is an interesting method, by which macromolecules and nanoparticles escape from the blood stream and specially gather more in tumors as opposed to in normal tissues. It happens most of the time in solid tumors, in which blood vessels are usually defective. Also, a faulty lymphatic drainage can lead to the loss of its ability to clear invading substances. These recognizing anatomical and pathophysiological characteristics of solid tumors have been for the most part used in tumor targeting. A large variety of nanoparticles utilize the enhanced permeation and retention (EPR) effect while intrinsic and physical stimuli as well as various nanomaterial properties and surface modification for cellular routing. Be that as it may, passive targeting is chance-dependent. Hence, active targeting, particularly molecular targeting, has been the area of concern in drug delivery research of late. Up to date, various surface markers have been found on abnormal cells or around their microenvironment. Integrins, folate, growth factors, and cytokines enhance the possibilities for counter-ligand functionalized drug vehicles to detect cells and tissue targets. With the capacity to bind to particular surface markers, circulating drug carriers may have a higher inclination to attach and accumulate at the site of cancer cells. Likewise, various cell-penetrating molecules have been found to enhance the drug delivery efficiency.[41] Undoubtedly, the combined effect of both active and passive targeting for drug delivery can produce amplified results.

This review paper will focus on using nanotechnology for targeted drug delivery systems addressing challenges facing the fight against cancer therapy. A number of issues are raised which include: immune reactions, drug resistance, biological hurdles (micro environment of tumor tissues), treatment affecting healthy cells, cancer drugs being cleared from the body by reticulo-endothelium system (RES) before reaching target point and recurrence of cancer.

Table. 1: A summary of the merits and demerits of nanomaterials conjugated to targeting moieties.

Nanomaterial	Advantages	Disadvantages	References
Liposomes	Biodegradable, Biocompatible, and Flexible Can form capsules and as well as deliver both watery andlipid-soluble medications The drugs Are delivered at a particular site and also Facilitate sustained release of drugs Drugs encapsulated are protected from unfriendly environmental conditions	They have a short half-life and relatively weak stability The carriers are usually leaky in nature and form into solid when they fuse together Carriers which carry lipids experience oxidation and hydrolysis Some liposomal constituents can lead to	[13, 42-44]

	regulates the pharmacokinetics and pharmacodynamics of an encapsulated drugs	allergic reaction in some patients There can a situation whereby these liposomes can accumulate outside target tissues	
Polymers	It is relatively more stable than liposomes Drugs are delivered at a particular site as Well as facilitating controlled release of drugs Due to its multifunctional nature targeted drug delivery and imaging is enhanced It uses both enhanced permeability and retention effect to accumulate in cancer cells First pass metabolism can be avoided in that it explores different route of administration Regulates the pharmacokinetic properties of an encapsulated drugs	Problems such toxicity Is a big challenge most Especially the nonbiodegradable polymers Only a limited number of these polymers are used in clinical trial Unmodified nanoparticles are easily cleared by MPS Due to its large surface area, handling them becomes a little bit problematic	[45-47]
Dendrimers	Pharmacokinetics behavior are reproducible in that they are usually uniform They are water- soluble and do lead to any untoward side effect Drugs can be conjugated to it due to the fact that they have various surface groups that can be Functionalized for targeting They prevent nucleic Acid degradation by forming dendriplexes Can encapsulate a wide variety of drugs They accumulate in tissues through passive targeting	Due to their high cationic charge density, it can lead to liver and nonspecific cytotoxicity accumulation Dendrimers with very Low molecular weight are easily cleared as compared with the ones with high molecular weight The Release profile of encapsulated drugs are poor	[48-54]
Quantum DOTS	Possess relatively stable photochemical as compared to dyes Size can be varied due to tunable spectrum Can be applied In the area of theranostics Dynamic imaging is enhanced because it is resistant to photobleaching	It can be toxic Colloidal instability There can a situation whereby these quantum dots can be taken up nonspecific organs and Cells As at now there is no data on reproducibility and quantification	[17,46]
Carbon Nanotubes	It has a large surface area that can be modified It does not lead to any untoward side effect It is relatively easy to scale-up industrial production Oligosaccharides are Protected from degrading when they are circulation Drugs can be loaded in tube-haped structures It can be conjugated with a wide variety of drugs with ease	Its solubility in water is Poor Has an unfavorable pharmacokinetic profile Cannot be metabolized by the body	[18, 55, 56]

Triggered Drug Delivery By Stimuli-Sensitive Nanoparticles: For a drug to come into the market space from its synthesis through to clinical trials, it can take about 15 years with a cost of more than $500 million.[57] Nonetheless, most of these medications experience the ill

effects of side effect, poor adsorption, poor solubility, high medication dosing, minimum efficiency, and uncontrolled, non-specific delivery with high cytotoxicity, which constrain their uses. For chemotherapeutic medications, the worry ought to be more noteworthy in light of the fact that the vast majority of the anticancer medications are exceptionally toxic to the healthy cells and harm the healthy cells alongside the cancer cells, which brings about unwanted reactions in the body.[58] These issues can be overcome and toxicity can be decreased if the medications are delivered through a vehicle that conveys the medications exactly on request. To accomplish the exact mission, we require a drug delivery system (DDS) that conveys the medications to our target cells without influencing the healthy cells in a controlled way.[59,60] This is exactly what stimuli-sensitive drug delivery systems seek to achieve.

Nicolò Mauro et al delivered a twofold system organized with graphene oxide-containing nanogels as photothermal operators for the treatment of colorectal malignancy. Hyaluronic acid/polyaspartamide-based twofold system nanogels utilized as potential treatment for colorectal malignancy. Graphene oxide, on account of the enormous aromatic surface zone, permits to effectively load high measure of irinotecan (33.0% w/w) and gives to the system hyperthermic properties when irradiated with a near infrared (NIR) laser beam. The release of antitumor medication is affected both by the pH of the outside medium and the NIR light process. In vitro biological experiment on human colon cancer cells (HCT 116), uncovered that nanogels are taken-up by the disease cells and, within the sight of the antitumor medication, and could deliver a synergistic hyperthermic/cytotoxic impact. At long last, 3D tests showed that it is conceivable to conduct thermal ablation of solid tumors after the intra-tumoral administration of nanogels.[61]

For example, Wang et al designed a general technique to accomplish photoreactions in view of triplet-triplet annihilation up conversion (TTA-UC) and Förster resonance energy transfer (FRET). PLA-PEG micellar nanoparticles containing in their centers hydrophobic photosensitizer and annihilator atoms which, when animated with green light, would experience TTA-UC. The upconverted energy was then transferred by FRET to a hydrophobic photocleavable group (DEACM), which was at the core. The DEACM was clung to (and consequently inactivated) the cell-binding peptide cyclo-(RGDfK), which was bound to the PLA-PEG chain. Cleavage of DEACM by FRET reactivated the PLA-PEG-bound peptide and enabled it to move from the molecule center to the surface. TTA-UC

followed by FRET permitted photo controlled binding of cell attachment with green light LED irradiation at low irradiance for brief periods. These are appealing properties in photo-triggered systems.[62]

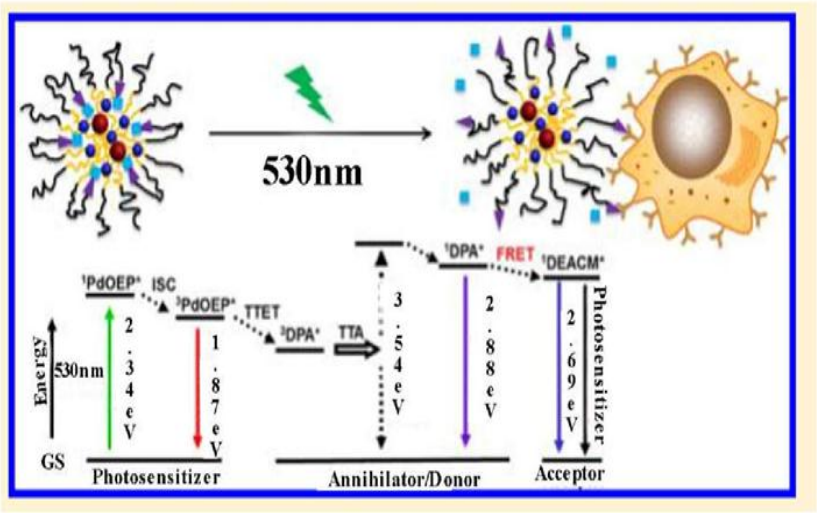

Fig. 1: Efficient Triplet-Triplet Annihilation Based Up conversion For Nanoparticle Phototargeting. Reproduced with permission from reference (62) (Wang et al). Copyright 2018 American Chemical Society.

No endeavor has been made to investigate thermo-responsive polymers for medicate conveyance at nearer to the tumor tissue temperature and furthermore convey drugs within the intracellular compartment. Along these lines, the improvement of new polymer scaffolds that are equipped for conveying drugs at 40-43 °C and totally inactive at ≤37 °C would be extremely helpful to upgrade the local drug concentration at tumor tissue over normal healthy tissues. Kashyap et al outlined double responsive polymer nano-scaffolds for directing anticancer medications both at the tumor site and intracellular compartments. The double responsive polymer scaffold was observed to be fit for loading water insoluble medications like doxorubicin (DOX), and fluorescent probe-like Nile Red. The medication release kinetics uncovered that DOX was protected in the core shell assembly at typical body temperature (beneath LCST, ≤ 37 °C). At nearer to diseased tissue temperature (above LCST,~43 °C), the polymeric scaffold experienced burst release to convey 90% of loaded medications inside 2 h. At the intracellular condition (pH 7.4, 37 °C) within the sight of esterase enzyme, the amphiphilic copolymer ruptured in a slow and controlled way to discharge >95% of the medications in 12 h. In this way, both burst release of cargo at the tumor microenvironment and control delivery at intracellular compartments were proficient

in a solitary polymer system. Cytotoxicity assay of DOX-loaded polymer were performed on breast (MCF-7) and cervical tumor (HeLa) cells. Among the two cell lines, the DOX-loaded polymers indicated improved termination in breast tumor cells. Moreover, the cell take-up of the DOX was examined by confocal and fluorescence microscopy. The present research describes another enzyme and thermal responsive polymer scaffold approach for DOX delivery in cancer cells.[63]

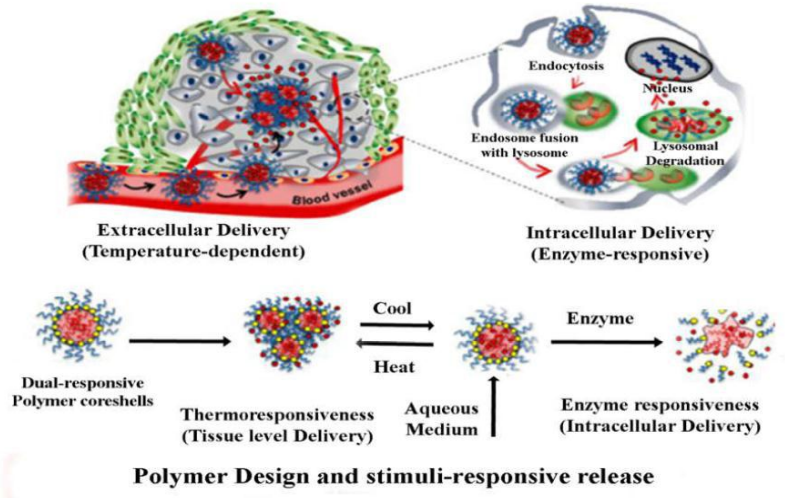

Fig. 2: Enzyme and Thermal Dual Responsive Amphiphilic Polymer Core-Shell Nanoparticle to Treat Cancer Cells. Reproduced with permission from reference (63) (Kashyap et al). Copyright 2018 American Chemical Society.

Examples of stimuli-responsive nanotherapeutics

Stimulus factor	Non-formulation	Active-compound	Cancer cells	Reference
Magnetic Resonance	Supramolecular nanofibres	Pemetrexed	Glioma	[64]
Electric field	Citrate-Apatite Nanocrystals with carbonate	bleomycin hydrochlorid	MCF-7 cells	[65]
Redox potential	HCN polymeric nanoparticles	Camptothecin	HER2 positive cancer cells	[66]
light	Chitosan-based nanoparticles	5-aminolaevulinic acid	Oral cancer cells	[67]
pH	Multifunctional metal-phenolic nanoparticles	Doxorubicin	Hep G2 cells	[68]

Methods Used for Targeted Drug Delivery

Targeted Drug Delivery: Conventional chemotherapy can result in uncontrolled distribution of anticancer medications, which can cause harmful side effect in healthy cells and tissue.[21,69,70] Hence, it is imperative to create a drug delivery system with the aim of binding to disease cells while healthy cells are avoided.[25,71] A number of biomolecules, including hyaluronic acid (HA)[72,73] folic acid[74], peptides[75], and monoclonal antibodies[76] have been produced as targeting ligands for specific receptors on cancer cells.

Influence of the architecture of actively-targeted NPs: The conjugation of ligands on the surface of NPs changes their characteristics.[77,78] They lose both their rotational and translational freedom to free molecules, the new targeted element accomplishes enhanced avidity on account of increased valency.[79-81] Correspondingly, the properties of the NP like size, geometry, surface properties (charge and hydrophobicity), and composition (NP material) likewise influence the behavior of the targeted constructs. To completely comprehend the properties of actively-targeted NPs, it is imperative to determine how the physicochemical properties of the NPs influence the interactions with the targets.

The ligand density: Since an increased valency permits cooperative effects, the density of the targeting molecules on the surface of NPs greatly affects the impact of their affinity for the substrate. Thermodynamically, the binding of a ligand to its substrate can result to binding of its neighbors inclusive.[81,82] Biologically, the several interactions of the NP with the cell membrane force the clustering and local concentration of receptors. Subsequently, the membrane is wrapped and internalized. All these impediments detach the NP from the cell surface which results in an increased avidity. This permits the utilization of various relatively low affinity ligands to effectively bind targets with high avidity.[83] In vitro, an increased ligand density improves cell take-up.[84] Be that as it may, this increase in affinity is not generally linear. At times, the helpful impact of the ligand can saturate and further increments in ligand density can effectively affect cell binding.[85,86] This effect can be clarified in view of improper orientation of the ligand, steric prevention of neighboring molecules or competitive behaviors for the binding of the receptor.

The NP size and shape: Size and shape of the nanomaterial must be mulled when designing targeted NPs. Spherical particles and smaller sizes presents with higher curvatures can be hazardous for post-synthesis ligand functionalization.

Surface and ligand charge: From a synthesized point of view, the charge of the unfunctionalized NP and that of the ligand can influence the conjugation yield and the spatial display of the ligand on the surface.[87] Both repulsive as well as attractive forces between the surface of the NPs and the ligand can affect with their conjugation[87,88] or ultimately, influence the final ligand structure and conformation. PEG is mostly used to diminish the effect; however this can result in an increase in final particle size and also complicate synthesis.[85] The last surface charge will influence the therapeutic effect of the targeted on NPs. In spite of the interaction between cationic NPs and negatively charged cell membrane, the NP demonstrates an increase in cellular binding and uptake abilities, in a non-specific manner.[89] Since most ligands are charged molecules, the NP surface charge is dependent on the ligand densities, materials, and NP formulation strategies.

Surface hydrophobicity: Other than surface charge, hydrophobicity can likewise influence the architecture of the ligand display.[84] This can have genuine impacts since most polymeric NPs have hydrophobic cores.[90] The last surface hydrophobicity of the NPs can likewise influence non-specific interactions with cells. From one viewpoint, actively targeted NPs without steric stabilization appear to lose their substrate-binding capability when proteins adsorb on their surface.[91] Then again, while PEG surface-functionalization can defer adsorption of opsonins what's more, plasma proteins, the utilization of long or dense PEG chains can likewise keep ligands from achieving their targets.

Ligands Used for Targeted Drug Delivery: Riboflavin (RF) is an important vitamin for cellular metabolism. Lately, it has been demonstrated that RF is internalized through RF transporters which are exceptionally over-expressed by prostate and breast tumor cells, and additionally by angiogenic endothelium. Beztsinna et al exhibited an enhanced synthesis protocol for making tailor-made amphiphilic phospholipid-based RF derivatives utilizing phosphoramidite chemistry. In vitro take-up investigations demonstrated that RfdiC14-containing liposomes were unequivocally internalized in HUVEC, PC3, and A431 cells, in a specific manner.[92]

In another development HA, a begning, biodegradable, naturally occurring polysaccharide, has been widely joined with drug carriers since it has a high binding ability toward its essential receptor, CD44, which is over-expressed on various sorts of tumor cells (e.g., breast, ovarian, and lung cells).[93-96] Nonetheless, HA-based carriers can likewise have nonspecific interaction with normal cells, which can lead to a decrease in targeting specificity toward

cancer cells. To solve this issue is to join low-fouling materials, for example, poly (ethylene glycol) (PEG)[97,98], into targeted carriers in order to prevent any interaction between these health cells and diminish uptake by phagocytes thereby improving circulation in-vivo.

A metal-phenolic capsule with high targeting and low nonspecific cell binding properties has been developed by Ju et al. The capsules were made by covering phenolic-functionalized hyaluronic acid (HA) and poly (ethylene glycol) (PEG) on calcium carbonate template, accompanied by cross-connecting the phenolic groups with metal ions and expelling the template. The joining of HA fundamentally improved binding and interaction with a CD44 overexpressing (CD44+) cancer cell line, while the incorporation of PEG decreased nonspecific association with a CD44 minimal expressing (CD44-) cell line. Besides, high specific targeting to CD44+, cells can be adjusted with low nonspecific binding to CD44- cells basically by utilizing an optimized feed-ratio of HA and PEG to change the content of HA and PEG joined into the capsule. Loading an anticancer medication (i.e., doxorubicin) into the acquired capsule brought about fundamentally higher cytotoxicity to CD44+ cells yet bring down cytotoxicity to CD44-cells.[99]

Aptamers

It is characterized as a short DNA or RNA or an even peptide molecule that has affinity for a specific receptor on the tumor cell. Basically, aptamers can be classified into two

1. DNA or RNA aptamers: They are usually short strands of oligonucleotides.
2. Peptide aptamers: They consist of one or more short variable peptide domains, attached at both ends to a protein scaffold.

On account of their exceptional conformational structures that begin from intramolecular Watson-Crick interactions, Aptamers demonstrate high affinity and specificity. Candidates are screened from extensive oligonucleotide libraries with random sequences by exploiting the nucleic acid sequence. Binders are selected and specifically enhanced at the expense of non-binders utilizing the polymerase chain response. Aptamers that bind strongly to small molecules and proteins have been identified. The biggest advantage of Aptamers is their ability to isolate high affinity ligands against a number of substrates, however they possess other advantages, thus their reproducible synthesis and simplicity of their chemical derivatives give room for Aptamers to be used as ligands for targeted NPs.[100]

Abnous et al, developed a novel chemotherapy drug- free DNA nanocomplex made up of three medicinal aptamers (IDA, AS1411 and apMNK2F) intended for treatment of cancer cells. The MTT assay revealed, PC-3 and 4T1 cells are target cells and CHO cells are non-target cells both treated with apMNK2F-AS1411-IDA complex (DNA nanocomplex), together with AS1411, IDA and apMNK2F alone. Internalization of apMNK2FAS1411-IDA complex was investigated by fluorescence imaging and flow cytometry analysis. In the last stride, the introduced DNA nanocomplex was applied to prevent cancerous growth *in vivo*. The after effects of the internalization assay revealed that the created apMNK2F-AS1411-IDA complex was internalized into PC-3 and 4T1 cells, however not into CHO cells. The after effects of internalization assay were affirmed by MTT assay. apMNK2F-AS1411-IDA complex was more cytotoxic in PC-3 and 4T1 cells (target) and less cytotoxic in CHO cells (non-target). Likewise, the DNA nanocomplex could viably smother the development of tumors *in vivo*.[101]

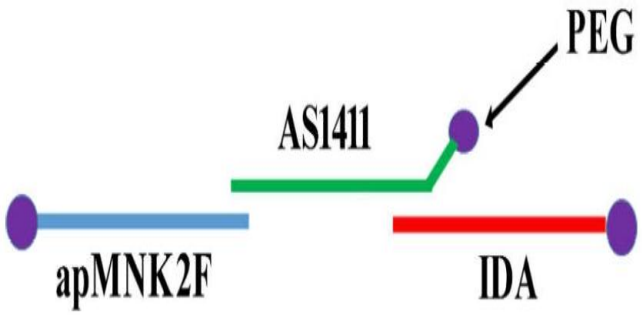

Fig. 3. A Novel Chemotherapy Drug-Free Delivery System Composed Of Three Therapeutic Aptamers For The Treatment Of Prostate And Breast Cancers In-Vitro And In-Vivo.

Reproduced with permission from reference[102] (Abnous et al). Copyright 2018 Elsevier Inc.

Affibodies

These are small proteins engineered to bind to a large number of cancer tissues with high affinity, imitating monoclonal antibodies. They are therefore a member of the family of antibody mimetics. These molecules are used as biopharmaceutical drugs for cancer therapy.

Tyrosine Kinase receptor HER3 has become a therapeutic target in various cancers including prostate, breast and ovarian because it can activate the P13K/Akt pathway by dimerization with HER2 and also mediating drug resistance. An improved efficacy of HER3-targeted

therapeutics would consequently profit an extensive variety of patients. This investigation by Schardt et al assessed the capability of multivalent presentation, through protein engineering. It was used to improve the viability of HER3-targeted affibodies as contrasting options to monoclonal counter acting agent therapeutics. Evaluation of multivalent affibodies on an assortment of malignant cell lines uncovered their expansive capacity to enhance inhibition of Neuregulin (NRG)- induced HER3 and Akt phosphorylation contrasted with monovalent analogs. Designed multivalency prevented cell growth by affibodies as single agent and also as part of combination treatment techniques. Mechanistic investigations uncovered that designed multivalency improved affibody-mediated HER3 downregulation in different tumor cell types. By and large, these outcomes feature the guarantee of engineered multivalency as a general method for improved therapeutic effect of HER3-focused on therapeutics against a number of cancers.[103]

Another study by Hoppmann et al, showed a straightforward and generalizable methodology for lessening the renal uptake of Affibody molecules while sustaining their tumor uptake. Radiolabeled DOTA-HSA-$Z_{HER2:\,342}$ conjugates showed specific cell uptake into SKOV3 cell cultures. Positron emission tomography (PET) examinations were performed in SKOV3 tumor-bearing mice utilizing ^{64}Cu-DOTA-HSA-$Z_{HER2:\,342}$. High tumor uptake values (>14% ID/g at 24 and 48 h) and high liver concentrations as well as low kidney concentrations were noticed. Biodistribution studies and single-photon emission computed tomography (SPECT) examinations utilizing ^{111}In-DOTA-HSA-$Z_{HER2:\,342}$ validated these outcomes. At 24 h post injection, the biodistribution information uncovered high tumor (16.26% ID/g) and liver (14.11% ID/g) concentrations and generally low kidney concentration (6.06% ID/g).[104]

Monoclonal Antibodies: Monoclonal antibodies thus mAb or moAb are antibodies that are made by indistinguishable immune cells that are all clones of a unique parent cell. These antibodies have specific affinity to cancer cells making them helpful as against polyclonal antibodies with numerous epitopes. Anhorn et al, developed a target-oriented nanoparticle in light of biodegradable human serum albumin (HSA) loaded with cytostatic drug doxorubicin. The surface of the nanoparticles was covalently modified by attaching trastuzumab. HER2 overexpressed breast cancer cells showed high cellular up-take as well as binding of these nanoparticles. The specific transport of the cytostatic drug doxorubicin with this nanoparticulate formulation into the HER2 overexpressing breast cancer cells, their release, and biological activity was demonstrated. The outcomes showed that these cell-type specific

drug-loaded nanoparticles could enhance tumor therapy.[105] Monoclonal antibody (RG 7155) developed by Ries et al and this monoclonal antibody is used to block CSF-1 receptor one of the known proto-oncogenes. In-vivo study revealed that CSF-1 blockade diminishes $F4/80^{+}$ tumor-associated macrophages.[106]

Peptides: Peptides are either natural biological or artificially fabricated short chains of amino acids monomers connected by peptide bonds. Peptides can be incorporated into drugs to convey drugs at the cancer tissue or cell. Due to their shorter chains they can be made to form smaller molecular sizes and simpler three-dimensional structures thereby easing up synthesis and conjugation, enhancing their stability and making them resistant to the environment. The stated advantages above, in combination with improved screening techniques to isolate ligand-substrate have contributed immensely to the role of peptides as targeting moieties in the past decade. Arginine-glycine-aspartic (RGD) is a motif found on a number extracellular matrix (ECM) and plasma proteins.[107] RGD gained much attention in research when it was found out that it has specific binding sites for fibronectin (FN) and the FN receptor.[108] Laminin, vitronectin (VN), fibrinogen (Fg), von Willebrand factor (vWF), osteopontin etc are glycoproteins found in ECM and they serve us RGD-adhesive proteins.[109] RGD is vital in both cell recognition and cell adhesion and has been utilized in both tumor therapy and tissue engineering by either recombinant means or chemical methods. By chemical means RGD-peptides and RGD-mimetics can be used to restyle liposomes, polymers and peptides so that therapeutic agents would have a better biological response. Additionally, RGD-peptides were utilized in gene delivery by viral and non-viral vectors.[110]

Advantages: There are 2 types of RGD-containing peptides based on structure and sequence and they are linear and cyclic RGD peptides. Cyclic RGD peptides are preferred over the linear RGD peptides due to their higher activity. The merits of cyclic peptides are that they have higher affinity for integrin receptors and also resist proteolysis.[111,112] RGD peptides possess some advantages us targeting agent for cancer therapy[113,114]: (i) RGD is smaller in nature and easier; (ii) the use of RGD reduces immune reactions; (iii) synthesis of RGD peptides is relatively simple and inexpensive, makes it easier to be translated into clinical trials; RGD has important regulatory functions in many biological activities they are; actin formation in skeletal muscle, cell attachment, focal-adhesion formation with integrins, and cell spreading.[115]

A phenomenal method developed by Kumal et al was used to convey a platinum (IV) medication to prostate cancer cells by developing glutathione-stabilized (Au@GSH) gold nanoparticles. Glutathione (GSH) is known for its antioxidant properties, which inhibit cancer cells. Due to its antioxidant properties as well as its high surface-area-to-volume ratio of Au@GSH NPs was able to convey platinum (IV) drug by targeting it to its receptor thus neuropilin-1 receptor (Nrp-1). A lethal dose of a platinum (IV) drug coupled with the Nrp-1-targeting peptide (CRGDK) was able to specifically deliver to prostate disease cells *in vitro*. The targeted peptide binds specifically to the Nrp-1 receptor, prompting improved cell take-up and cell toxicity levels. These nanocarriers were nontoxic, however displayed high cytotoxicity and an increase in therapeutic effect when functionalized with a targeting peptide and medication. The uptake of drug-loaded nanocarriers depended on the interaction with Nrp-1 in cell lines expressing high (PC-3) as well as low (DU-145) levels of Nrp-1, as affirmed *via* inductively coupled plasma mass spectrometry and confocal microscopy. The nanocarriers have powerful anticancer action, through upregulation of nuclear factor kappa-B (NF-κB) protein (p50 and p65) expression and activation of NF-κB-DNA-binding activity.[116]

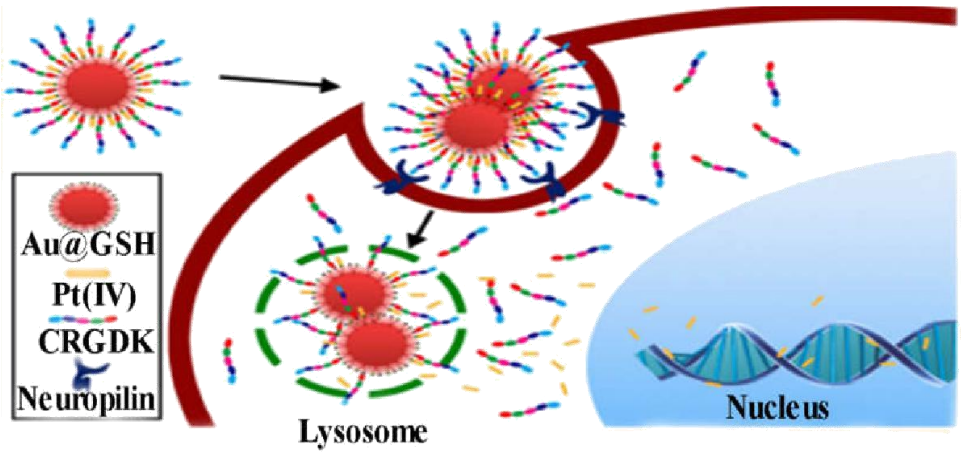

Fig. 4. Neuropilin-1-Targeted Gold Nanoparticles Enhance The Therapeutic Efficacy of Platinum (IV) Drug For Prostate Cancer Treatment. Reproduced with permission from reference[116] (Kumar et al) Copyright 2018 American Chemical Society.

Proteins: They consist of one or more polypeptides bound to ligands to target cancer cells. More often than not, proteins are used as small molecules to convey drugs to their target sites. However, proteins are often interchanged with peptides but what distinguish these two is on the basis of their size. A number of naturally-occurring proteins have endogenous targets that can be used for therapeutic purposes. The three-dimensional shape of proteins provides

affinity for specific substrates, and therefore non-antibody proteins can be used as targeting moieties.

Lipoprotein transport lipids in the human body. It is made up of lipoproteins, phospholipids, cholesterol esters, free cholesterol, and protein. The composition of lipoproteins in human body possesses chylomicrons, very low density lipoprotein (VLDL), low density lipoprotein (LDL), and high density lipoprotein (HDL). Lipoprotein-mimetics have gained interest in cancer therapy because it targets cells naturally and also minimal immune reactions. The main reason LDL and HDL identify the corresponding receptor of target cell is due to alipoproteins expressed on their surfaces. Lipoprotein receptor can be classified into lipoprotein receptor (LDLR) and scavenger receptor type A (SRA). Lipoprotein receptors are found on a number of tumor cells making it necessary as targeting for treatment and diagnosis. It is worth noting that lipoprotein receptors are also present on the surfaces of non-neoplastic diseases. Due diligence must be done when treating cancer cells so that cell toxicity can be reduced to the barest minimum. Ullal et al covalently conjugated small-molecule medication to a magnetic nanoparticle which was then utilized as a read-out for target expression and drug-binding affinity. Poly(ADP-ribose) polymerase (PARP) was used as an inhibition model framework, which was designed to deal with recognized differential expression of PARP in scant cells with astounding correlation to highest quality levels, the capacity to emulate drug pharmacodynamics *ex vivo* through competitive target drug binding, and the possibility to perform such measurements in clinical samples.[117]

Intracellular protein delivery is a critical tool for both therapeutic and basic applications. Successful protein delivery confronts two noteworthy difficulties: proficient cell take-up and avoiding endosomal sequestration. Herein, a general procedure for direct conveyance of useful proteins to the cytosol utilizing nanoparticle-stabilized capsules (NPSCs) was reported by Tang et al. These NPSCs are framed and stabilized *via* supramolecular cooperation between the nanoparticle, the protein cargo, and the fatty acid capsule interior. The NPSCs are ~130 nm in distance across and highlight low harmfulness and phenomenal stability in serum. The NPSCs were efficacious protein carriers which were exhibited through the delivery of completely utilitarian caspase-3 to HeLa cells with concomitant apoptosis. Conveyance of green fluorescent protein (GFP) affirmed cytosolic delivery and also intracellular targeting of the conveyed protein, exhibiting the utility of the system for both therapeutic and imaging applications.[118]

Inorganic Targeting Agents: Plasmon resonance (SPR) band on the surfaces of inorganic nanoparticles such as gold, silver and copper make them display brilliant colours.[119-123] The very reason why inorganic nanomaterials are so special for biomedical applications is due to the tunability of optoelectronic properties which is size and shape-dependent.[124-127] Silver has a long history for medicinal use.[128,129] It was used in world war II to treat burns.[130] Aside burns, silver nanoparticles can also be used as a biocide against microbial infections and diabetic skin ulcers.[128] The Ag+ ion present in silver nanoparticles contribute immensely in their biological activity. Platinum nanoparticles are not well known for their medicinal purposes, instead platinum compounds are known for their anti-tumor action (cis-platin and its derivatives).[131] The advantage of using platinum nanoparticle is when modified structural can minimize the cytotoxicity of drugs. Other inorganic nanoparticles include the use of metal oxides such as SiO_2 with functionalized surfaces and Fe_3O_4 (magnetic nanoparticles) as a vector for targeted delivery of drugs and genes with reasonably low toxicity.[132] These nanoparticles can be easily synthesized and well characterized in the lab. The boron and gadolinium nanoparticles can be used to treat cancer cells and also have neutron capture therapy (NCT).

Circumventing Major Drug Delivery Problems Through Enhanced Targeting

In spite of gigantic endeavors made toward finding novel materials and biomolecule markers for targeted drug delivery systems (DDS), not many of them are really specific after intravenous infusion and targeting is chance-dependent. Active and passive targeting techniques need exogenous medication vehicles to disperse and voyage in circulation for long to be able to go through the leaky vasculature or recognize the surface markers. Be that as it may, the circulating environment, in which many medication vehicles cannot have a sufficiently long circulating time to accomplish targeted binding, is amazingly complicated.[133,134] Moreover, the human body has an innate defense mechanism for invasion. For instance, the reticuloendothelial system (RES) quickly perceives foreign bodies and pulverizes them by well-rehearsed biological processes. The RES, likewise called the mononuclear phagocyte systems, includes essentially bone marrow progenitors, blood monocytes, and tissue macrophages.[135] Furthermore, the EPR impact is some way or another heterogeneous in the tumor microenvironments and differs among patients.[136] For instance, hypoxic locales of solid tumor for the most part don't display EPR impacts in view of poor angiogenesis.[137] Considering the complexity and sophistication of *in vivo* conditions, conventional active and passive targeting methods are woefully inadequate. Subsequently,

creating novel DDS with really specific targeting is an impressive test for current medicine and nanotechnology. In recent times, cellular backpacks are attached to drug loaded particles on cell surface thereby enhancing protection of therapeutic agents as well as protecting cellular integrity. These backpacks prevent RES elimination, off site release of drugs and finally improves retention time of drugs in circulation. Michael F. Rubner et al utilized unique properties of macrophages for targeted drug delivery. Herein, HA (hyaluronic acid) was used to coat macrophages which can strongly bind to CD44 receptor expressed in many cancer cells. Compared to the conventional spherical particles it was found out that flat PEM-based disk were able to attach themselves to cell surface as compared to the spherical disks. Ligand-receptor interaction is one beneficial strategy of attaching particles to circulating cells. Identifying surface markers and binding ligands would be very useful for ligand-based drug carrier design. However, binding efficiency and *in vivo* specific binding within blood circulation still remains big hurdle. Intelligent targeting agents are required to aid drugs to bypass the RES and target the required cells.

Reversing Multi-Drug Resistance Through Targeted Delivery

For an effective tumor treatment, there exist four extreme issues that should be attended to and one of such issues is multidrug resistance (MDR), the others are recurrence, late stage diagnosis and aggressive metastasis. MDR of cancer cells results in around 90% chemotherapeutic failure of patients with metastatic tumors, and along these lines it remains a challenge for a fruitful chemotherapy treatment of cancer. Typically, the MDR of tumor cells, caused by the malfunctioning of genes, for the most part originates from either intrinsic high expression of ATP-binding cassette (ABC) transporter proteins or acquired resistance in malignancy cells by the stimulation of anticancer medications to overexpress ABC transporters.[138-140] Novel nanotechnology-based methodologies toward treatment of MDR malignancies expect the engagement of nanoparticles keeping in mind the end goals which include increased intracellular medication accumulation, silence of efflux transporters genes and inhibiting MDR-related proteins and factors.[141]

In this a mussel-inspired engineering methodology by Jianxiang Zhang et al may quite advance cell take-up and tissue retention of NPs. In this methodology, the catechol moiety is covalently moored onto biodegradable NPs. In this way, created NPs can be adequately internalized by sensitive and multidrug resistant tumor cells, and some healthy cells, bringing about amazingly potentiated *in vitro* activity when an antitumor medication is packaged.

Additionally, the recently engineered NPs bear the cost of increased tissue retention post local or oral delivery. This biomimetic approach is promising for making utilitarian nanomaterials for medicate conveyance, immunization, and cell therapy.[142] Mix treatment utilizing proteins and small molecules gives access to synergistic treatment procedures. Rotello et al loaded paclitaxel into the hydrophobic center of the NPSC and self-gathered caspase-3 and nanoparticles on the capsule surface. The subsequent combination NPSCs indicated higher cytotoxicity than both of the single operating agent NPSCs, with synergistic activity set up utilizing combination index value. Simultaneous delivery of small molecule drugs and proteins reduce drug administration as a result of prevented multidrug resistance.[143]

Targeted Delivery for Theranostics

This term was coined to define ongoing efforts in clinics to develop more specific, individualized therapies for various diseases, and to combine diagnostic and therapeutic capabilities into a single agent. This innovation counteracts repeat of tumor in that a more exact diagnosis and treatment is established. Herein, the role of drug targeting agents can be described as pivotal. They are capable of orchestrating every single move which is picked up by the diagnostic system in and around the target cells. This means that a good theranostic system requires a highly efficient drug targeting agent for enhancement.

In this, a one of a kind sort of redox-sensitive NCPs was built with manganese ion (Mn2+) and dithiodiglycolic acid as the disulfide (SS)- containing organic bridging ligand. The Mn-SS NCPs when obtained with a mesoporous structure could be effectively loaded with doxorubicin (DOX), a chemotherapeutic agent. The yielded MnSS/DOX nanoparticles are covered with a layer of polydopamine (PDA) and after that modified by poly(ethylene glycol) (PEG). In such a Mn-SS/DOX@PDA-PEG NCP structure, the disulfide linkage (SS) inside dithiodiglycolic acid can be cleaved in the presence of glutathione (GSH), resulting in a proficient redox-responsive dissociation of NCPs following drug release. In the meantime, Mn2+ in Mn SS/DOX@PDA-PEG NCPs would offer a strong T1 contrast in magnetic resonance (MR) imaging, Upon intravenous injection, these Mn-SS/DOX@PDAPEG NCPs demonstrate effective tumor homing, as uncovered by MR imaging, and offer a clearly enhanced *in vivo* remedial result contrasted with that accomplished with free DOX by Zhuang Liu et al.[144]

Thus, a protein-polymer bio-conjugate-covered multifunctional upconversion nanosystem, Comprising of upconversion nanoparticles (UCNPs) center, custom-made amphiphilic protein-polymer bio-conjugate shell, and photosensitizer zinc phthalocyanine (ZnPc) as well as antitumor medication doxorubicin co-loaded inside, the nanomaterial was created for consolidated photodynamic treatment (PDT) and chemotherapy. In this framework, UCNPs core could change over entering near-infrared light to visible light for synchronous cell fluorescence imaging and photodynamic therapy by activating ZnPc to produce cytotoxic ROS, while the protective shell of bovine serum albumin poly (ε-caprolactone) (BSA-PCL) offered magnificent water solubility, great stability, and low cytotoxicity. The ROS creation test demonstrated that this nanosystem could effectively produce singlet oxygen under NIR irradiation. A cellular uptake study exhibited that extreme fluorescence outflow of the UCNPs could be seen in HeLa cells, demonstrating their real-time imaging capability. Essentially, the combined therapy UCNP system proved to be an enhanced tumor cell killing ability as compared to single PDT or chemotherapy system by Zhongyun Liu et al.[145]

In another specific circumstance, liposomes, artificially prepared from a lamellar phase lipid bilayer, have been presented as reasonable nano-carriers for UCNPs. Here, we made a hybrid nano-carrier comprising of Er3+ and Yb3+ co-doped NaGdF4 UCNPs that were encapsulated in the aqueous phase of the liposomes and the capability of the nano-carriers for drug delivery which appeared by co-loading the model anticancer medication doxorubicin (DOX). Under 980 nm excitation, a decline of the green up-conversion emission of the NaGdF4: Er3+, Yb3+ UCNPs was watched when DOX was co-loaded with the UCNPs in the liposome nanocarrier. This extinguishing impact is doled out to the energy transfer between the contributor UCNP and the acceptor DOX and is most critical, since it takes into consideration the spectral checking of the DOX loading and release from the liposome nano-carriers. Along these lines, the medication loading, release, and spectral observing properties of the liposome nano-carriers were altogether characterized enabling us to evaluate their future potential as theranostic nano-carriers. Huang et al.[146]

CONCLUSION AND FUTURE PROSPECT

Nanotechnology has helped to curb some of the problems listed above in the fight against cancer. It is worthy of note that not a single technology can easily prevent these problems. However, it is necessary that the individual technologies are harnessed to explore their advantages. Going to the future, a more combined approach can be looked at to tackle the

problems associated with the underlining problems that affect the fight against cancer cells. Most importantly, drug targeting should be pivotal in our quest for an ideal cancer therapy. Herein, we have offered a thorough discussion concerning site-specific targeting for enhanced drug delivery. Our review was able to outline the important aspects of drug delivery. We also pointed out the major problems that have been overcome with targeted delivery of drugs. It is an undeniable fact that researchers need to pay much attention in order to explore innovative ways to improve on the existing strategies to chauffeur drugs to the required destinations.

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COMPETING INTEREST

The authors declare that there are no competing interests.

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