Available online on 15.02.2019 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Review Article

Active targeting of nanoparticles: An innovative technology for drug delivery in cancer therapeutics

Dr. Rupalben K. Jani*[1], Gohil Krupa[2]

Department of Pharmaceutics, Parul Institute of Pharmacy and Research, Parul University, Waghodia-391760, Vadodara, Gujarat, India

ABSTRACT

In nanomedicines, currently a wide array of reported nanoparticle systems is being explored by targeting schemes which suggests great potential of targeted delivery to revolutionize cancer therapeutics. This review gives insight into recent challenges in modification of nanoparticle systems for enhanced cancer therapy acknowledged by researchers to date and also outlines different major targeting strategies of nanoparticle systems that have been utilized for the delivery of therapeutics or imaging agents, targeting ligand and cross-linking agent to cancer which was divided into three sections: 1) Angiogenesis associated targeting, 2) Uncontrolled cell proliferation targeting and 3) Tumor cell targeting.

Keywords: nanoparticles, tumor cells, active targeting, targeting strategies, targeting ligands

Article Info: Received 26 Dec 2018; Review Completed 24 Jan 2019; Accepted 29 Jan 2019; Available online 15 Feb 2019

Cite this article as:

Jani RK, Krupa G, Active targeting of nanoparticles: An innovative technology for drug delivery in cancer therapeutics, Journal of Drug Delivery and Therapeutics. 2019; 9(1-s):408-415

http://dx.doi.org/10.22270/jddt.v9i1-s.2356

***Address for Correspondence[1,2]:**

Department of Pharmaceutics, Faculty of Pharmacy, Parul Institute of Pharmacy and Research, Parul University, At Post-Limda, Ta-Waghodia, Dist-Vadodara, Gujarat, India. Pin: 391760

1. INTRODUCTION

Focusing on cancer, applied nanotechnology has been revolutionized in the field of cancer therapeutics with immense potential owing to recent advancements in nanoparticles (NPs) based drug delivery systems. The main goal of most nanoparticle (NP) system is to prevent the degradation of active therapeutic agents to achieve enhanced bioavailability and to regulate their pharmacokinetic profile. However, most drugs are associated with some limitations such as poor water solubility, improper size and surface area, biodistribution and targeting challenges, and low therapeutic index [1].

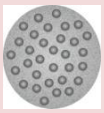
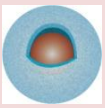
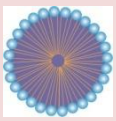
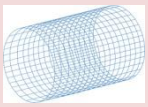
To overcome these shortcomings, scientists are always in search for the improved, structurally stable therapeutic NPs that offer several advantages over the free drug which can improve the efficacy of treatment and decreases the possibility of the serious side effects[2].

In general, due to their distinctive characteristics like enormous surface area, high drug loading capacity, long circulation time in blood, controlled drug-release capacity, minimal toxicity, biocompatibility, storage stability, and flexibility in the route of administration, NPs have become prominent candidates for optimized cancer therapy through site specificity, avoidance of multi drug resistance and the systematic delivery of an therapeutic agent.

1.1. Recent Nanoparticle systems for cancer therapy:

Recently there are several types of NPs are available for cancer treatment. Observing the development in the NPs in cancer disease treatments motivates the researchers to investigate its use in a various application such as protein NPs, liposomes, micelles, metallic NPs, carbon nanotubes, dendrimers, Protein- and peptide-drug conjugates, etc. [3, 4, 5, 6]. The formulation development of the NP systems in functional moieties based on its physical characteristics, therefore, the site targeting of the drug can be possible to enhance the stealth properties of the NPs such as calculating time enhancement and positively enhanced endocytosis the hydrophilic surfaces would be used [7, 8].Table 1 showing the Liposomes, Natural Polymers, Synthetic Polymers, Micelles, Dendrimers, Iron-Oxide NPs, Gold NPs which have been used for clinical trial.

Table 1: The NPs with its physical properties explored for the clinical development.

Commonly used NPs	Size of NP	Physical characteristics of NPs
Quantum Dots (Qds) [9]	2-10 nm 	high fluorescence quantum yield broad absorption spectra and, high photostability
Gold NPs [10]	1-100 nm 	They are high photo-thermal conversion rate, Gold Nanorods Intense light absorption. Different shapes and size are available. Good colloidal stability, biocompatibility and simple ligand conjugation chemistry.
Silica [11]	50-1000 nm 	Porous Silica NPs (Psi NPs) They have a large surface area with pore volume, have good thermal and chemical stability. They offers simple surface functionalization
Iron-Oxide NPs [12]	10-100 nm 	Super paramagnetic Iron-Oxide NPs (Spions) magnetic resonance imaging contrast agents use as clinical development, biodegradable, diverse formulations allow and Biocompatible
Micelles[13]	10-100 nm 	Hydrophobic core acts as natural carrier environment, structural modifications, Unique core-shell architecture.
Synthetic Polymers (PLGA)[14]	50-300 nm 	This drug easily incorporated in a matrix and synthetic material is FDA approved
Dendrimers[15]	5 – 20 nm 	Polyvalent, non-toxic, chemically stable, soluble and conjugation of the therapeutic agent.
Albumin as Natural Polymers[16]	50-300nm 	non-toxic, biodegradable and Biocompatible, chemically modify,
Carbon Nanotubes[17]	1-10nm 	high propensity, easily chemically modified, High carrying capacity
Liposomes[18]	20 – 1000 nm 	lipophilic drugs, stability in-vivo, protect drugs from breakdown, low uptake by macrophages .

1.1.1 Advantages of therapeutic Nanoparticles:

The key part of the NPs is to revert the bioactive molecules physicochemical characteristics to required bio pharmacologic profiles, control release of bioactive agents, enhanced the therapeutic drug delivery and efficiency also NPs perform theranostic functions.

Despite; the advantages offered by NPs, the challenges associated with it should be considered before formulating any therapeutic NPs; some of the challenges are as follows[13]

(i) Non-targeted NPs could easily be recognized by mononuclear phagocyte system (MPS) present in blood, liver, spleen, lung, and bone marrow.

(ii) Surface hydrophobicity of NPs is a key factor for enhanced blood components adsorption onto the NP surface.

(iii) Prolonged circulation time of NPs is a pre-requisite for in vivo administration until they reach the target site.

(iv) Localization of NPs to the tumor following enhanced permeability and retention (EPR) effect could be hindered by abnormal tumor structure leading to ineffective drug uptake.

1.1.2 These challenges can be overcome as follows:

Surface modification of the NPs with appropriate targeting moieties could overcome these challenges to some degree since targeting agents would competently carry the active molecule to its specific site of action rather than undesired localization [15]. This concept triggered the development of several approaches for structural modification of NPs. Although structural alterations of these NPs may control the reticulo endothelial system (RES) recognition via stealth mechanism, the efficacy of targeted NPs with definite progression has not been standardized yet. This review presents an overview of different NP targeting strategies with their advantages and limitations and recent challenges acknowledged by the researchers to date.

This review will particularly focus on different targets being targeted by NPs, the possible techniques performed to conjugate NPs with targeting agents, and their biological responses in both in vitro and in vivo studies[19].

Table 2 Clinical development of nanomedicines for tumor targeting

Bioactive compound	NP Formulation	Targeted ligand	Name of the drugs	Indication	Status
Doxorubicin	PEGylated liposomes	F(ab')2fragmentofhuman Ab GAH	MCC-465	Metastatic stomach cancer	Phase I
Doxorubicin	PeGylated liposomes	Antigen-binding fragments (Fab) of cetuximab	C225-ILS-DOX	Advanced solid tumors	
siRNA[20]	Cyclodextrin-based(21) NP containing anti-RRM2	Transferrin	CALAA-01	Various solid tumors	
siRNA[22]	Liposomes	Protein kinase N3	Atu027	Solid tumors	
p53 gene	Liposomes	Anti-transferrin receptor single-chain Ab fragment(TfRscFv)	SGT53	Solid tumors	
BikDD plasmid DNA	Liposomes	Proapoptotic gene	C-vISA-BikDD	Pancreatic cancer	
Docetaxel	PeGylated PL(G)A	Small molecule	BIND-014 (Accurins™)	Solid tumors	Phase II
Oxaliplatin	Liposomes	Transferrin	MBP-426	Gastroesophageal Adenocarcinoma	

1.2. NP Targeting Strategies

Conventional therapies are rapidly eliminated from the body and suffer from widespread distribution into nontargeted organs and tissues [12], whereas targeted therapeutic NPs have gained promising attention through offering a "therapeutic strategy" to tackle the requirements for frequent drug administration, higher dose, and unwanted toxicities related to the conventional therapies [11]. Therefore, an improvised treatment regimen with more patient convenience has become a necessity. Ideally, targeting refers to the specific localization of NPs to the desired site rather than indiscriminate distribution throughout the body. Before being accumulated to the diseased site, these targeted NPs are required to overcome external barriers, en route barriers, and cellular barriers [10]. Effective design of an ideal delivery system is the key foundation to overcome these barriers. There are two major tumor targeting strategies, passive and active targeting, that have been widely studied [17]. These two strategies are correlated and work to efficiently deliver the drug particles to the target site. Passive targeting takes advantage of the pathophysiological feature of the diseased tissue, commonly tumor, while active targeting of drug carrier initially utilizes the benefits of passive targeting to accumulate into the tumor region and subsequently bind to the target cells using targeting ligand that leads to receptor-mediated internalization of NPs into the cells[9].

1.2.1. Passive Targeting: Advantages and Challenges.

Passive targeting depends on tumor microenvironment, enhanced permeability and retention (EPR) effect, and tumor pH to deliver therapeutic agents from the nanocarriers. Passive drug targeting is widely exploited in cancer therapy because NPs circulating in the bloodstream can be localized to cancerous tissues through the well-known EPR effect and helps drugs to expose directly at the tumor tissue bypassing systemic metabolism [23, 24] Anatomically, inherent leaky tumor microvasculature is present in cancerous tissues which are characterized by abnormal branching and enlarged inter-endothelial gaps which results in breakdown of tight junctions between endothelial cells and a disrupted basement membrane[24]. This leaky and defective vascular architecture created due to the rapid vascularization and large gaps between endothelial cells which is a vital component to augment the neoplastic environment which is coupled with poor lymphatic drainage allows the famous EPR effect [25, 26]. Thus, EPR effect has become a guiding principle for the development of cancer targeting drug design.

But, EPR effect is involved with few challenges since macromolecules or NPs can invade into the tumor tissue only if they can avoid the RES and renal clearance. A drug should remain at least 6 hours in the circulation to get accumulated into the neoplastic tissues via EPR effect [27]. EPR effect was reported unsuccessful to maintain stable circulation of NPs in the bloodstream due to size restrictions of the tumor fenestrations.

The development of therapeutic nanocarriers with enhanced retention time is still under practical challenge, particularly in clinical tumors, where the blood vessel morphology is very different than that of mice model used in preclinical studies. This could limit the intra tumoral distribution of NPs [28]. In addition, the blunt localization and accessibility of drug carriers into the tumor might not be feasible in case of certain tumors (lung cancer). The high interstitial pressure of solid tumors does not allow homogenous distribution of drugs in the tumor

Recently, scientists are developing NPs that can adapt the tumor microenvironment to selectively target cancer cells. There are several NP formulations in preclinical and clinical trials that are able to tackle the microenvironment through inhibiting angiogenesis, suppressing tumor growth factors, and enhancing several immune cells (T cell, NK cells, and dendritic cells) [29]. Despite the challenges, realistic clinical settings are necessary to obtain the benefit of the applied NP treatment.

To date, there are several FDA approved NPs such as Doxil (1995), Feridex (1996), Mylotarg (2000), Zevalin (2002), Abraxane(2005,2013), Oncospar(2006), and Ontac (2008) that utilize enhanced permeability and retention (EPR) effect to accumulate in solid tumors [30]

1.2.2. Active Targeting: Advantages and Challenges.

The term “active targeting” defines a cell-specific targeting ligand-receptor interaction by coupling with drug or nanocarrier with or without using cross-linking agents at the target site after reaching via blood circulation and extravasation. These targeting moieties have specific affinity for the cell surface antigens (e.g. receptors)and they can differentiate between normal and tumor cells based on the receptor or antigen expression levels(29). For example, using Herceptin targeted NPs helped to differentiate human epidermal growth factor receptor 2 (EGFR), human epidermal receptor-2 (HER2) positive and (HER2) negative breast cancer cells. Clearly, the active targeting of HER2 receptors on the over-expressed cells with NPs was confirmed[30].

However, active targeting drug delivery system has many limitations such as very difficult to predict the effectiveness of the active targeted drug, very poor penetration in tumor site, to manage NPs complexity and very poor familiarity regarding the physiologic and biological structure of the tumor. Although, this treatment has main advantages to use vascular targeted NPs which can be used to cure or protect the problems in the target drug delivery system[31].

1.2.3 Active targeting strategy for development site-directed NPs

As discussed in the above sections the passive targeting has many limitations to accumulated the drug at the site locations, therefore, the research and development is further going on the active targeting to reach the maximum effectiveness in the targeting drug delivery system [32, 33]. To improve accumulation of the drug into the tumor site the polymeric NPs are the versatile solution because it has multifunctional structures which can be modified [34, 35]. The modification of the ligand surface and little changes in the polymeric composition leads the targeting effectiveness in concerned biological systems. The various types of affinity ligands were used in active targeting which can help into the NPs binding, can be used as antigens and they act differently in diseased tissue and plasma membrane[36]. In addition to this such drug delivery system can be used as intracellular or extracellular compartment controlled released drug. Therefore, the primary function of the targeting ligand is to cell internalization by active targeting NPs, enhanced the NPs uptake into the targeted cell and enhanced the therapeutic efficacy. The biodistribution is majorly related to NPs colloidal properties, therefore, the enhancement of cell uptake at target sites and cell recognition would be possible through the targeting ligands. The clinical trials are currently in the progress for the widely accepted active targeting drug delivery systems [37, 38].

2. TARGETING RECEPTORS FOR CANCER THERAPY:

2.1 Angiogenesis-associated targeting receptors

Angiogenesis is the physiologic process by which new blood vessels are formed from pre-existing vessels which involves tight regulation of several signaling pathways. It occurs primarily during human development and enhanced permeability and retention (EPR) production; though, abnormal regulation of angiogenesis process was also found in various pathologic conditions, including cancer.

Targeting receptors coupled with angiogenesis in malignancies mainly involves integrins and vascular endothelial growth factor (VEGF) molecule and its associated VEGF receptors[39]. Among Vascular Endothelial Growth Factor Receptors (VEGFR), VEGFR-2 plays a significant role in angiogenesis and highly expressed frequently in human cancers. Integrins ($\alpha_v\beta_3$and others) belongs to a vast family of hetero dimeric transmembrane cell-adhesion receptors which have been a NP preferentially expressed on the angiogenic endothelium in malignant tissues.

The angiogenesis targeting has become a wider area of interest for cancer therapeutics as it is known to cause the invasion, migration, and proliferation of smooth muscle and endothelial cells, which results in degradation of the basement membrane and formation of a new lumen structure. Thus, angiogenesis appears to be one of the most critical steps in tumor transformation to the metastatic form, having the ability to spread to other parts of the body[40].

The main angiogenic targets investigated for NP systems for therapeutic benefit includes various receptors involved in malignancies are the VEGFRs, $\alpha_v\beta_3$ integrins, Matrix Metallo-Proteinase Receptors (MMPs), and Vascular Cell Adhesion Molecule-1 (VCAM-1).

2.2 Vascular endothelial growth factor receptor (VEGFR)

VEGFR induces the tumor angiogenesis significantly, therefore, the development of the antibodies, peptide and any methods for targeting to the VEGFR. It has also the potential to function as a targeting receptor in prostate and breast cancer. In neoplastic cells, the oncogenes and Tumor hypoxia regulate VEGF, therefore, VEGFR-1 and VEGFR-2 upregulated[41].

2.3 $\alpha_v\beta_3$ Integrin

Hetero dimeric transmembrane endothelial cell-adhesion receptors include the $\alpha_v\beta_3$ integrin as one of the family members. The targeting strategy for the $\alpha_v\beta_3$ integrin has centered non-peptide mimetic. The ligand for the drug delivery induced by the non-peptide mimetic, non-peptidomimetics coupled to a NP for anti-angiogenesis

therapies[42]. Generally, endothelial cells producing in neovascular endothelial which is producing the angiogenesis and increase the endothelial cell interaction and locomotion [43]. The $\alpha_v\beta_3$ integrin intrinsically associated with calcium-dependent signaling and VEGFR-2 signaling would be helpful in the endothelial cell migration. The important outcome of the research is that integration of the $\alpha_v\beta_3$ integrin with the active targeting leads the treatment efficiency and enhanced the anti-angiogenic treatments[44].

2.4 Vascular cell adhesion molecule (VCAM)

VCAM-1 binds integrins to extracellular matrix proteins during the angiogenesis and relocation of the tumor. The VCAM-1 expressed on the endothelial cells surface and it was closely appears to various cancer cell metastasis and helps in the cell to cell adhesion. VCAM-1 expression increased in cancer which is linked to leukemias and lymphomas. This includes the lung, renal cell carcinoma, Hodgkin's disease, nephroblastoma, B-cell lymphocytic leukemia and breast cancer[45]. First time targeted in vivo study of VCAM-1 based on immuno-liposomes[46] and its results state that the accumulation is extensive in the endothelial cells in mice tumor[47].

In addition to this VCAM-1 targeting has localized liposomes tumor vasculature. The lower degree of the localization was found in VCAM-1 targeting in localize liposomes in tumor vasculature in comparison to non-specific liposomes. Fluorescence microscopy could find the tumor sections where immuno-liposomes were found. Non-targeted liposomes lower fluorescence intensity because of the dilution of liposomes throughout the tumor and high degree of extravasations [48].

2.5 Matrix metalloproteinase

Structurally related zinc-dependent endopeptidases include the matrix metalloproteinase (MMPs). In this degradation of an extracellular matrix similar to vascular cell adhesion molecule-1 and αvβ3 integrin. The fundamental physiological MMPs component used for repairs the tissue, angiogenesis, and morphogenesis[49]. In addition to this, it also plays a key role in pathological conditions of tumor metastasis. The MMPs major function in NP system is activated to MMP-2 by membrane type-1 MMP [50]. Membrane type-1 MMP plays a significant role in migration, degradation of extracellular matrix, capillary tubes formation, recruitment of accessory cells and endothelial cell invasion. They are attached with the angiogenesis and metastasis, therefore, it was noticed that it is overexpressed in certain types of tumor cells, breast, lung, gliomas, and cervical carcinomas. Finally, membrane type-1 MMP enhanced the binding activities of the ligand by utilizing the αvβ3 integrin[51].

3. UNCONTROLLED CELL PROLIFERATION TARGETING RECEPTORS

In cancer, cell proliferation receptors play an important role to enhance the cancer tumor; therefore, these receptors are to be targeted in cancer therapeutics. The active targeting is mostly used to target cell proliferation receptors[52]. Basically, there are four monoclonal antibodies targeting criteria such as an antigen is overexpressed by the cancer cell, antigen participates in the cancer disease, the stability of antigen is depending upon the tumor cell surface and antigen can be classified in a variety of tumor cell and expressed by a huge percentage[53]. There are several actively targeting NPs were used as folate receptors, transferrin receptors, human endothelial receptors.

3.1 Human epidermal receptor (HER)

The HER is basically tyrosine kinases group member. These receptors offer highly up-regulated targets to the tumor cell surface. The HER -2 and epidermal growth factor receptor (EGFR) are investigated in the tyrosine kinases family receptors. These receptors have potential in the cancer therapy as binding the endogenous growth factor ligand and mediate a cell for its growth. Amphiregulin, Epidermal Growth Factor, Epiregulin and Betacellulin are the endogenous EGFR ligand and they are used as targeting methods [54]. The high growth of the EGFR in the solid tumor indicates the advanced stage of the tumor and it is EPR effect presenting the metastatic capabilities in different cancer. In the various tumor such as in colorectal, breast, brain cancers and breast epidermal growth factor receptor is overexpressed in these tumors. For the neck and head cancer the Cetuximab, a monoclonal antibody cancer treatment is recently used[55] and its performance can be improving by combination with growth factor receptor therapy. Recently the HER-2 is widely used for mAb-based therapeutic strategies as attractive targeting[56]. Trastuzumab, a monoclonal antibody is designed and developed for antagonizing HER -2 function and approved the FDA.

3.2 Transferrin receptors

Transferrin receptors are nothing but the serum non-heme iron-binding glycoprotein and it is a very important type of receptor for cancer treatment because it can help to transport iron to proliferating cells[57]. The direct interaction of the transferrin receptors to its ligand transferrin or monoclonal antibodies mAbs specific, placental tissue, rapidly proliferating cells, endothelial cells of the blood-brain barrier[58] are the important factor of this transferrin receptor. The transferrin receptors when binds upon the cell surface at that time transferrin is endocytosed into acidic compartments. The transferrin receptors are also available for the human clinical trials such as Diphtheria toxin, Cisplatin and Adriamycin[59].

3.3 Folate receptors

The 38 kDa glycosyl-phosphatidylinositol-anchored glycoprotein is a folate receptor. This receptor is found highly in the research area for the treatment of cancer. The density of the folate receptor increases when the advanced stage cancer is detected which can improve the targeting efficiency and restricts or reduces the cancer tumor disease[60]. Therefore, the polarized epithelial apical membrane binding with the folate receptor can help I the tumor targeting also can help to protect the healthy cells. In folate, the antibodies and folic acid are used as targeting ligand. These receptors are nontoxic, inexpensive, non-immunogenic, stable in storage, easy to conjugate to carriers, retain high binding affinity.

The folate receptors have potential in many types of cancer such as breast cancer, lung, head, neck, brain and renal cell. The doxorubicin and paclitaxel have folate receptor-targeted liposomes which can be used to avoid the multidrug folate receptor as a chemotherapeutic agent[61].

4. TUMOR CELL TARGETING RECEPTORS

The research data of American Cancer Society cancer statistics state that the maximum death of human being by the various types of cancer in 2008. They have estimated that the 40,930,161840,49960 and 28660 death due to breast, lung, colorectal and prostate cancer respectively[62].

To cure cancer there are various methods described in the angiogenesis sections for tumor cell targeting and

uncontrolled cell proliferation. However, there are many other targeting methods for the particular cancer treatment such as the NPs systems are specifically coupled with particular cancer rather than universal cancer.

4.1 Targeting to breast cancer

The human epidermal receptor-2 used as targeting to the breast cancer is one of the oldest technologies as drug delivery. The Trastuzumab is a monoclonal antibody is approved by the FDA in 1998 to act against HER-2. The HER-2 positive tumor can be cured by the Targeted poly NPs with the model toxin[63]. In breast cancer, quantum-dot loaded chitosan NPs and cross-linked human serum albumin NPs are provide effective treatment with HER -2 targeting.

The folate receptors are also used as cancer treatment and it can improve the effect on tumor site. In breast cancer cell the targeted folic acid-conjugated PEGylated magnetite NPs entered easily in comparison to the surface of non-PEGylated NPs. The paclitaxel-loaded NPs with lactic acid and ethylene glycol gave an improvement in anticancer activity and cell internalization. Luteinizing hormone-releasing hormone receptor can be used to detect the metastasized and localized breast cancer and widely used as an anticancer agent and targeted delivery. The luteinizing hormone-releasing hormone conjugated super-paramagnetic iron oxide with luteinizing hormone-releasing hormone positive cell help in separation of the NPs which is segregated in the liver[64].

4.2 Targeting colorectal cancer

The development of many antibodies for the treatment of colorectal cancer is available. Panitumumab, Cetuximab and Avastin antibodies approved by FDA in the year of 2004 to 2006. Avastin, Panitumumab and Cetuximab antibodies are humanized monoclonal which act against the HER-1, EGFR and VEGF and used for the advanced colorectal cancer. These approved antibodies have potential as targeting drug delivery system and give advancement in the nanocarriers. During the delivery of payloads, it produces the synergetic effects and inhibiting cancer pathways.

Targeting moieties interact with cancer cell in colorectal cancer, therefore, this development is most viable and considered as novel development for colorectal cancer. Guanylyl cyclase C receptors are used for the metastatic and localized colorectal cancer which considered the novel targeting approach because it interacts and overexpressed with the bacterial enterotoxins of colorectal cancer cells.

Moreover, for the batter treatment in colorectal cancer the polymeric conjugates have been used.

4.3 Targeting to prostate cancer

In the prostate cancer, the prostate-specific membrane antigens are the main targeted antigen in the prostate cancer treatment which is also known as overexpressed cancerous tissue. The prostate specific membrane antigen efficiently working in the LNCaP prostate cancer cell line and it is class II transmembrane glycoprotein. The aptamers specific to prostate specific membrane antigen used as the targeting and found anticancer agent in the prostate cancer as per the research data available from the MIT and Harvard.

The current development in the surface modification of the NPs enhances the targeting efficiency. Aptamers surface density range is well defined therefore it enhance tumor targeting but it was observed that its effects to protective PEG shells. Also, it can be rapid to isolate the NP in the spleen and liver. Prostate specific membrane antigen is also well known as bind folate ligands prostate cancer targeting. to target the prostate cancer Folate-conjugated lipid NPs have been used. Other receptors such as Sigma receptors would be used as targeting receptor in prostate cancer and finally enhanced the therapeutic efficiency[65].

5. CONCLUSION

Application of various targeted NP system promises for more effective delivery to the region of interest which has resulted in the development of novel multifunctional delivery methods to treat cancer. NP systems have the ability to target various portions of the tumor utilizing specific targeting moieties, optimize the loading and optimally improve the release of nanocarrier and thus EPR effect problems associated with multi-drug resistance. Moreover, most of the targeting moieties provide synergistic antitumor effects as there is a large overlying in the types of targets. The research for more molecular targets needs to be undertaken to advance the ability of targeted nanocarrier which could alter biodistribution by enhancing overall efficacy and specificity of nanocarrier at the tumor site and decreases toxicity to normal tissue.

REFERENCES

1. Haley B, Frenkel E. NPs for drug delivery in cancer treatment. Urologic oncology. 2008;26(1):57-64.
2. Kukowska-Latallo JF, Candido KA, Cao Z, Nigavekar SS, Majoros IJ, Thomas TP, et al. NP targeting of anticancer drug improves therapeutic response in animal model of human epithelial cancer. Cancer research. 2005;65(12):5317-24.
3. Lalani R, Misra A, Amrutiya J, Patel H, Bhatt P, Patil SK. Approaches and Recent Trends in Gene Delivery for Treatment of Atherosclerosis. Recent patents on drug delivery & formulation. 2016;10(2):141-55.
4. Bellocq NC, Pun SH, Jensen GS, Davis ME. Transferrin-containing, cyclodextrin polymer-based particles for tumor-targeted gene delivery. Bioconjugate chemistry. 2003;14(6):1122-32.
5. Janib SM, Moses AS, MacKay JA. Imaging and drug delivery using theranostic NPs. Advanced drug delivery reviews. 2010;62(11):1052-63.
6. Vhora I, Patil S, Bhatt P, Misra A. Protein- and Peptide-drug conjugates: an emerging drug delivery technology. Advances in protein chemistry and structural biology. 2015;98:1-55.
7. Betancourt T, Brown B, Brannon-Peppas L. Doxorubicin-loaded PLGA NPs by nanoprecipitation: preparation, characterization and in vitro evaluation. Nanomedicine (London, England). 2007;2(2):219-32.
8. Lowery AR, Gobin AM, Day ES, Halas NJ, West JL. Immunonanoshells for targeted photothermal ablation of tumor cells. International journal of nanomedicine. 2006;1(2):149-54.
9. Danhier F, Feron O, Preat V. To exploit the tumor microenvironment: Passive and active tumor targeting of nanocarriers for anti-cancer drug delivery. Journal of controlled release : official journal of the Controlled Release Society. 2010;148(2):135-46.
10. Elsabahy M, Wooley KL. Design of polymeric NPs for biomedical delivery applications. Chemical Society reviews. 2012;41(7):2545-61.
11. Nie S, Xing Y, Kim GJ, Simons JW. Nanotechnology applications in cancer. Annual review of biomedical engineering. 2007;9:257-88.
12. Pejchal R, Doores KJ, Walker LM, Khayat R, Huang P-S, Wang S-K, et al. A Potent and Broad Neutralizing Antibody Recognizes and Penetrates the HIV Glycan Shield. Science. 2011;334(6059):1097.
13. Singh R, Lillard JW, Jr. NP-based targeted drug delivery. Experimental and molecular pathology. 2009;86(3):215-23.
14. Yoo D, Lee JH, Shin TH, Cheon J. Theranostic magnetic NPs. Accounts of chemical research. 2011;44(10):863-74.
15. Ulbrich K, Holá K, Šubr V, Bakandritsos A, Tuček J, Zbořil R. Targeted Drug Delivery with Polymers and Magnetic NPs: Covalent and Noncovalent Approaches, Release Control, and Clinical Studies. Chemical Reviews. 2016;116(9):5338-431.

16. Fernandez-Fernandez A, Manchanda R, McGoron AJ. Theranostic applications of nanomaterials in cancer: drug delivery, image-guided therapy, and multifunctional platforms. Applied biochemistry and biotechnology. 2011;165(7-8):1628-51.
17. Mohamed F, van der Walle CF. Engineering Biodegradable Polyester Particles With Specific Drug Targeting and Drug Release Properties. Journal of Pharmaceutical Sciences. 2008;97(1):71-87.
18. Lee DE, Koo H, Sun IC, Ryu JH, Kim K, Kwon IC. Multifunctional NPs for multimodal imaging and theragnosis. Chemical Society reviews. 2012;41(7):2656-72.
19. Tandel H, Bhatt P, Jain K, Shahiwala A, Misra A. In-Vitro and In-Vivo Tools in Emerging Drug Delivery Scenario: Challenges and Updates. 2018. p. 19-42.
20. Patil S, Bhatt P, Lalani R, Amrutiya J, Vhora I, Kolte A, et al. Low molecular weight chitosan–protamine conjugate for siRNA delivery with enhanced stability and transfection efficiency. RSC Advances. 2016;6(112):110951-63.
21. Bhatt P, Lalani R, Vhora I, Patil S, Amrutiya J, Misra A, et al. Liposomes encapsulating native and cyclodextrin enclosed paclitaxel: Enhanced loading efficiency and its pharmacokinetic evaluation. International Journal of Pharmaceutics. 2018;536(1):95-107.
22. Patil S, Lalani R, Bhatt P, Vhora I, Patel V, Patel H, et al. Hydroxyethyl substituted linear polyethylenimine for safe and efficient delivery of siRNA therapeutics. RSC Advances. 2018;8(62):35461-73.
23. Maeda H, Wu J, Sawa T, Matsumura Y, Hori K. Tumor vascular permeability and the ENHANCED PERMEABILITY AND RETENTION (EPR) effect in macromolecular therapeutics: a review. Journal of controlled release : official journal of the Controlled Release Society. 2000;65(1-2):271-84.
24. Carmeliet P, Jain RK. Angiogenesis in cancer and other diseases. Nature. 2000;407(6801):249-57.
25. Danquah MK, Zhang XA, Mahato RI. Extravasation of polymeric nanomedicines across tumor vasculature. Advanced drug delivery reviews. 2011;63(8):623-39.
26. Bazak R, Houri M, Achy SE, Hussein W, Refaat T. Passive targeting of NPs to cancer: A comprehensive review of the literature. Molecular and clinical oncology. 2014;2(6):904-8.
27. Chipman SD, Oldham FB, Pezzoni G, Singer JW. Biological and clinical characterization of paclitaxel poliglumex (PPX, CT-2103), a macromolecular polymer-drug conjugate. International journal of nanomedicine. 2006;1(4):375-83.
28. Bae YH, Park K. Targeted drug delivery to tumors: myths, reality and possibility. Journal of controlled release : official journal of the Controlled Release Society. 2011;153(3):198-205.
29. Siegler EL, Kim YJ, Wang P. Nanomedicine targeting the tumor microenvironment: Therapeutic strategies to inhibit angiogenesis, remodel matrix, and modulate immune responses. Journal of Cellular Immunotherapy. 2016;2(2):69-78.
30. Vieira DB, Gamarra LF. Advances in the use of nanocarriers for cancer diagnosis and treatment. Einstein (Sao Paulo, Brazil). 2016;14(1):99-103.
31. Riehemann K, Schneider SW, Luger TA, Godin B, Ferrari M, Fuchs H. Nanomedicine--challenge and perspectives. Angewandte Chemie (International ed in English). 2009;48(5):872-97.
32. Davis ME, Chen ZG, Shin DM. NP therapeutics: an emerging treatment modality for cancer. Nature reviews Drug discovery. 2008;7(9):771-82.
33. Petros RA, DeSimone JM. Strategies in the design of NPs for therapeutic applications. Nature reviews Drug discovery. 2010;9(8):615-27.
34. Nicolas J, Mura S, Brambilla D, Mackiewicz N, Couvreur P. Design, functionalization strategies and biomedical applications of targeted biodegradable/biocompatible polymer-based nanocarriers for drug delivery. Chemical Society reviews. 2013;42(3):1147-235.
35. Byrne JD, Betancourt T, Brannon-Peppas L. Active targeting schemes for NP systems in cancer therapeutics. Advanced drug delivery reviews. 2008;60(15):1615-26.
36. Kamaly N, Xiao Z, Valencia PM, Radovic-Moreno AF, Farokhzad OC. Targeted polymeric therapeutic NPs: design, development and clinical translation. Chemical Society reviews. 2012;41(7):2971-3010.
37. Lammers T, Kiessling F, Hennink WE, Storm G. Drug targeting to tumors: principles, pitfalls and (pre-) clinical progress. Journal of controlled release : official journal of the Controlled Release Society. 2012;161(2):175-87.
38. Shi J, Xiao Z, Kamaly N, Farokhzad OC. Self-assembled targeted NPs: evolution of technologies and bench to bedside translation. Accounts of chemical research. 2011;44(10):1123-34.
39. Vhora I, Patil S, Bhatt P, Gandhi R, Baradia D, Misra A. Receptor-targeted drug delivery: current perspective and challenges. Therapeutic delivery. 2014;5(9):1007-24.
40. Allen TM. Ligand-targeted therapeutics in anticancer therapy. Nature reviews Cancer. 2002;2(10):750-63.
41. Brown LF, Berse B, Jackman RW, Tognazzi K, Manseau EJ, Senger DR, et al. Expression of vascular permeability factor (vascular endothelial growth factor) and its receptors in adenocarcinomas of the gastrointestinal tract. Cancer research. 1993;53(19):4727-35.
42. Lalani RA, Bhatt P, Rathi M, Misra A. Abstract 2063: Improved sensitivity and in vitro efficacy of RGD grafted PEGylated gemcitabine liposomes in RRM1 siRNA pretreated cancer cells. Cancer research. 2016;76(14 Supplement):2063-.
43. Li L, Wartchow CA, Danthi SN, Shen Z, Dechene N, Pease J, et al. A novel antiangiogenesis therapy using an integrin antagonist or anti-Flk-1 antibody coated 90Y-labeled NPs. International journal of radiation oncology, biology, physics. 2004;58(4):1215-27.
44. Hood JD, Bednarski M, Frausto R, Guccione S, Reisfeld RA, Xiang R, et al. Tumor regression by targeted gene delivery to the neovasculature. Science. 2002;296(5577):2404-7.
45. Ruoslahti E. Fibronectin and its integrin receptors in cancer. Advances in cancer research. 1999;76:1-20.
46. Bhatt P, Lalani R, Mashru R, Misra A. Abstract 2065: Anti-FSHR antibody Fab' fragment conjugated immunoliposomes loaded with cyclodextrin-paclitaxel complex for improved in vitro efficacy on ovarian cancer cells. Cancer research. 2016;76(14 Supplement):2065-.
47. Osborn L, Hession C, Tizard R, Vassallo C, Luhowskyj S, Chi-Rosso G, et al. Direct expression cloning of vascular cell adhesion molecule 1, a cytokine-induced endothelial protein that binds to lymphocytes. Cell. 1989;59(6):1203-11.
48. Dienst A, Grunow A, Unruh M, Rabausch B, Nor JE, Fries JW, et al. Specific occlusion of murine and human tumor vasculature by VCAM-1-targeted recombinant fusion proteins. Journal of the National Cancer Institute. 2005;97(10):733-47.
49. Genis L, Galvez BG, Gonzalo P, Arroyo AG. MT1-MMP: universal or particular player in angiogenesis? Cancer metastasis reviews. 2006;25(1):77-86.
50. Sato H, Takino T, Miyamori H. Roles of membrane-type matrix metalloproteinase-1 in tumor invasion and metastasis. Cancer science. 2005;96(4):212-7.
51. Deryugina EI, Bourdon MA, Jungwirth K, Smith JW, Strongin AY. Functional activation of integrin alpha V beta 3 in tumor cells expressing membrane-type 1 matrix metalloproteinase. International journal of cancer. 2000;86(1):15-23.
52. Scallon BJ, Snyder LA, Mark Anderson G, Chen Q, Yan L, Weiner LM, et al. A Review of Antibody Therapeutics and Antibody-Related Technologies for Oncology. Journal of Immunotherapy. 2006;29(4):351-64.
53. Bhatt P, Vhora I, Patil S, Amrutiya J, Bhattacharya C, Misra A, et al. Role of antibodies in diagnosis and treatment of ovarian cancer: Basic approach and clinical status. Journal of controlled release : official journal of the Controlled Release Society. 2016;226:148-67.
54. Laskin JJ, Sandler AB. Epidermal growth factor receptor: a promising target in solid tumours. Cancer treatment reviews. 2004;30(1):1-17.
55. Patel J, Amrutiya J, Bhatt P, Javia A, Jain M, Misra A. Targeted delivery of monoclonal antibody conjugated docetaxel loaded PLGA NPs into EGFR overexpressed lung tumour cells. Journal of microencapsulation. 2018;35(2):204-17.
56. Pan X, Wu G, Yang W, Barth RF, Tjarks W, Lee RJ. Synthesis of cetuximab-immunoliposomes via a cholesterol-based membrane anchor for targeting of EGFR. Bioconjugate chemistry. 2007;18(1):101-8.

57. Rainov NG, Soling A. Technology evaluation: TransMID, KS Biomedix/Nycomed/Sosei/PharmaEngine. Current opinion in molecular therapeutics. 2005;7(5):483-92.
58. Gandhi M, Bhatt P, Chauhan G, Gupta S, Misra A, Mashru R. IGF-II-Conjugated Nanocarrier for Brain-Targeted Delivery of p11 Gene for Denhanced permeability and retention (EPR)ession. AAPS PharmSciTech. 2019;20(2):50.
59. Faulk WP, Taylor CG, Yeh CJ, McIntyre JA. Preliminary clinical study of transferrin-adriamycin conjugate for drug delivery to acute leukemia patients. Mol Biother. 1990;2(1):57-60.
60. Low PS, Antony AC. Folate receptor-targeted drugs for cancer and inflammatory diseases. Advanced drug delivery reviews. 2004;56(8):1055-8.
61. Shmeeda H, Mak L, Tzemach D, Astrahan P, Tarshish M, Gabizon A. Intracellular uptake and intracavitary targeting of folate-conjugated liposomes in a mouse lymphoma model with up-regulated folate receptors. Molecular cancer therapeutics. 2006;5(4):818-24.
62. Tan WB, Jiang S, Zhang Y. Quantum-dot based NPs for targeted silencing of HER2/neu gene via RNA interference. Biomaterials. 2007;28(8):1565-71.
63. Yewale C, Baradia D, Patil S, Bhatt P, Amrutiya J, Gandhi R, et al. Docetaxel loaded immunoNPs delivery in EGFR overexpressed breast carcinoma cells. Journal of Drug Delivery Science and Technology. 2018;45:334-45.
64. Tseng CL, Wang TW, Dong GC, Yueh-Hsiu Wu S, Young TH, Shieh MJ, et al. Development of gelatin NPs with biotinylated EGF conjugation for lung cancer targeting. Biomaterials. 2007;28(27):3996-4005.
65. Zhang Y, Zhang J. Surface modification of monodisperse magnetite NPs for improved intracellular uptake to breast cancer cells. Journal of colloid and interface science. 2005;283(2):352-7.