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Review

Bio-vehicles of cytotoxic drugs for delivery to tumor specific targets for cancer precision therapy

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ABSTRACT

Abnormal structural and molecular changes in malignant tissues were thoroughly investigated and utilized to target tumor cells, hence rescuing normal healthy tissues and lowering the unwanted side effects as non-specific cytotoxicity. Various ligands for cancer cell specific markers have been uncovered and inspected for directional delivery of the anti-cancer drug to the tumor site, in addition to diagnostic applications. Over the past few decades research related to the ligand targeted therapy (LTT) increased tremendously aiming to treat various pathologies, mainly cancers with well exclusive markers. Malignant tumors are known to induce elevated levels of a variety of proteins and peptides known as cancer "markers" as certain antigens (e.g., Prostate specific membrane antigen "PSMA", carcinoembryonic antigen "CEA"), receptors (folate receptor, somatostatin receptor), integrins (Integrin αvβ3) and cluster of differentiation molecules (CD13). The choice of an appropriate marker to be targeted and the design of effective ligand-drug conjugate all has to be carefully selected to generate the required therapeutic effect. Moreover, since some tumors express aberrantly high levels of more than one marker, some approaches investigated targeting cancer cells with more than one ligand (dual or multi targeting). We aim in this review to report an update on the cancer-specific receptors and the vehicles to deliver cytotoxic drugs, including recent advancements on nano delivery systems and their implementation in targeted cancer therapy. We will discuss the advantages and limitations facing this approach and possible solutions to mitigate these obstacles. To achieve the said aim a literature search in electronic data bases (PubMed and others) using keywords "Cancer specific receptors, cancer specific antibody, tumor specific peptide carriers, cancer overexpressed proteins, gold nanotechnology and gold nanoparticles in cancer treatment" was carried out.

1. Background

Cancer is a disease with high complexity resulting in abnormal random responses to a variety of cellular signals. Such ambiguous responses disturb many important cellular processes as proliferation and cell death. As a result, abnormal tumor cells accumulate and invade or damage the other surrounding tissues i.e., metastasis [1]. Several types of therapies have been used to treat cancer as radiotherapy, chemotherapy and surgical removal of tumors. Most of the anti-tumor drugs used as cancer chemotherapy are unable to differentiate between tumor and normal cells (not selective), thus resulting in devastating side effects, such as weakened immune system, loss of hair and diarrhea. Hence, researchers in the pharmaceutical field have been working on developing chemotherapeutic drugs with higher efficacy and lowered toxicity to the non-tumor healthy cells [2].

One hundred years ago, the Nobel prize winner, Paul Ehrlich created the foundation of targeted therapy by postulating the "magic bullets" to be implemented in fighting against human diseases [3].

Applying a similar concept, scientists have been seeking for an anti-cancer drug that can be "shoot" into the human body and hits only the targeted tumor cells, thus restricting its cytotoxic effect to the tumor site i.e. targeted cancer therapy [4]. The targeted cancer therapy requires first, a unique target in the tumor cells (either not or rarely found in the normal cells). Second, the drug has to be highly active exclusively at the tumor site. Several mechanisms have been proposed employing variety of cancer specific proteins/receptors to be targeted via specifically

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binding ligands known as Ligand Targeted Therapy (LTT). Some of the recently used ligands in targeted cancer therapy are summarized in Table 1. The process of ligand-receptor binding is linked to a phenomenon known as receptor mediated endocytosis frequently addressed in LTT to allow ligand conjugated drug penetration to the cell [5].

Generally, targeted delivery of anti-cancer drugs to the site of tumor cells can be either passive targeting by employing tumor vasculature characteristics, or active targeting based on the specific binding of the anti-cancer agents to its targeted molecules. Here in, a concise overview of the latest developments in targeted cancer therapies are presented highlighting some lately utilized examples of ligand mediated targeted therapy.

1.1. Characteristics of the receptors selected for Ligand targeted therapy (LTT)

To achieve the therapeutic effect of LTT, several important criteria have to be fulfilled with respect to the targeted receptors. ***Firstly,*** they have to be highly expressed on the tumor cells compared to the surrounding normal cells [6,7] Several cancer specific receptors are known to be overexpressed in certain types of cancer such as epidermal growth factor (EGF) receptor, prostate-specific membrane antigen (PSMA; also

Table 1
Summary of some ligands utilized lately in targeted cancer therapy.

Target	Targeting Ligand	Agent	Cancer Model	Ref
Epidermal growth factor receptor "EGFR"	A low-affinity anti-EGFR antibody drug conjugate (ADC), RN765C.	Anti-EGFR antibody linked to PF-06380101, a potent anti-mitotic agent.	Multiple cell line and patient-derived xenograft models, including EGFR-directed tyrosine kinase inhibitors resistant ones.	[192]
	Human epidermal growth factor bispecific angiotoxin (eBAT)	Consisting of human EGF (targeting EGFR), human amino terminal transferase (ATF is the high affinity binding moiety of human urokinase, targeting uPAR), and genetically modified Pseudomonas exotoxin	A variety of sarcoma and carcinoma cells that overexpress EGFR and urokinase plasminogen activator receptor uPAR	[193]
	Cetuximab, an epidermal growth factor receptor (EGFR) inhibitor.	Cetuximab conjugated with chemotherapy drug Docetaxel	Human epidermoid carcinoma (A431) xenograft	[194]
	Nanobody D10	$^{99\,m}$Tc-labeled D10 nanobody for SPECT tumor visualization	Human mammary (MDA-MB-468) and epidermoid (A431) carcinoma xenografts	[195]
	EGF (EGF-PEG-DSPE)	EGFR-targeted lipid polymeric nanoparticles (LPNs) consisted of cisplatin (CDDP) and doxorubicin (DOX) and an outer layer of EGF-PEG-DSPE ligand.	lung carcinoma cell lines and xenograft models.	[196]
	Her2/neu receptor	DNA nanospindles loaded with Daunorubicin (DNA-NS-DR).	Breast cancer (MCF-7) cells.	[197]
Prostate-specific membrane antigen "PSMA"	(PSMA)-binding tracers.	Radiolabeled 64Cu-PSMA ligands.	C4–2 cells, a subline of the PSMA positive cell line LNCaP, and a C4–2 tumor-bearing mouse model.	[198]
	PSMA-1, a prostate-specific membrane antigen (PSMA) targeting ligand.	PSMA-1conjugated to gold nanoparticles "AuNPs" for targeted-radiosensitization.	PC3pip "PSMA positive" and PC3flu "PSMA negative" cells.	[59]
Human epidermal growth factor receptor-3 "HER-3"	7E3, an anti-Neuregulin 1 (NRG1) antibody.	7E3 promotes antibody dependent cellular cytotoxicity in NRG1-positive cells and blocks NRG1-mediated HER3 activation.	Pancreatic tumor cells (PC) and cancer-associated fibroblasts (CAFs) and orthotopic pancreatic tumor xenografts.	[199]
Folate receptor α	Folate	A folate-conjugated DOTAP: Chol NP system (FNP) encapsulating the chemotherapeutic drug, cisplatin (CDDP), and human antigen R (HuR)-targeted siRNA.	Non-small cell lung cancer (NSCLC) cell lines (H1299 and A549).	[120, 200]
		folic acid (FA) and fluorescein isothiocyanate (FITC) molecules conjugated to a central poly (ethylene glycol) (PEG).	Rat hepatoma (N1S1) and human monocytic (U937) cell lines.	[201]
		folate liposomes of 5FU made from Dipalmitoylphosphatidylcholine (DPPC) conjugated with phosphatidyl choline (PC)	HT-29, Caco-2, HeLa and MCF-7 cell lines.	[202]
		crosslinked polyethylenimine nanogel particles loaded with Gadolium and copper sulfide targeting folate receptors "Gd/CuS@PEI-FA-PS NGs".	Cancer cells overexpressing FA receptor.	[203]
Transferrin receptor	Transferrin	transferrin-guided polycarbonate-based polymersomal doxorubicin (Tf-Ps-Dox)	Transferrin receptor (TfR)-positive human liver tumor SMMC-7721 model.	[151]
		Poly glutamic acid "PGA"-Asp-maleimide-cisplatin-peptide "transferrin receptor (TFR)-targeting peptide" complex (PAMCP).	HeLa tumor cells and Kun Ming (KM) mice.	[204]
	DT7 peptide (D(HRPYIAH))	Docetaxel "DTX" -loaded DT7-liposomes.	Hepatocellular carcinoma.	[205]
Death receptor 5 "DR5"	DR5 agonist antibodies	nanobodies (Nbs) against the DR5 ectodomain.	PC3, HeLa, and Colo205 are human cancer cell lines, LLC1 mouse lung cancer cell line.	[206]
	TNF-related apoptosis-inducing ligand (TRAIL)	TLY012 is an engineered human TNF-related apoptosis-inducing ligand (TRAIL)	Human primary dermal fibroblasts (HDFs), Skin biopsies healthy persons and patients with systemic sclerosis or morphea.	[207]
Programmed cell death receptor 1 (PD-1)	Programmed death-ligand 1 (PD-L1)	PD-L1 monoclonal antibody-conjugated miR-130a/oxaliplatin-loaded immunoliposomes	HGC27-bearing tumor xenograft model	[208]
	Anti-PD-1 antibody	Anti-PD-1 antibody	Syngeneic and orthotopic glioblastoma "GBM" models.	[208]
B-cell maturation antigen (BCMA)	CD3 bispecific antibody	antibody drug conjugate (ADC)	Myeloma cell lines and orthotopic myeloma xenograft models.	[209]
	anti-BCMA antibody	GSK2857916, an anti-BCMA antibody conjugated to microtubule-disrupting agent monomethyl auristatin F.	Patients with relapsed and refractory multiple myeloma.	[210]
glypican-3 (GPC-3) protein	Glypican-3 (GPC3) binding peptide (GBP)	GBP on the surface of a Fe3O4 Core/Au shell nanocomplex (FANP).	HepG2 tumor xenograft model.	[211]

known as FOLH1), and hepatocyte growth factor receptor [8–10]. However, the level of upregulation differs from one type to another. For example, CD30 is 4.4-fold higher expressed in anaplastic large cell lymphoma, whereas in breast cancer, the overexpression of receptor tyrosine protein kinase ERBB2 (also known as HER2) is only two-fold higher [11,12]. Usually, to ensure efficient therapeutic effect of LTT, it is considered sufficient when the level of receptor expression is about three-fold higher than in normal non-tumor cells. Such elevated level of expression provides higher delivery of the targeted anti-cancer drug to the tumor cells than the normal cells, which might be due to the higher cancer cell division rate compared to the non-tumor cells [13,14].

Furthermore, it is well known that in tumorigenic cells the rate of receptor recycling is usually higher thus supplying a constant high receptor level to be recycled and thus repeated cycles of binding to the ligand drug conjugate and endocytosis are possible as explained in Fig. 1 [15,16].

Secondly, location of the targeted receptor: higher expression of the cancer specific receptor is pivotal for LTT but it will not be efficient if it is not accessible for ligand binding. Thus, the receptor employed in LTT is favored to be exposed on the cell surface for ligand binding and easily reached. Furthermore, the ideal target receptor should not be detached from the cell and shed into circulation since this may cause the release of the cytotoxic drugs away from the tumor resulting in unwanted side effects [17,18].

Thirdly, specificity of the selected receptor: It is important to have a cancer cell specific receptor in LTT, which binds with high affinity to its specific ligand and/or ligand drug complex. Furthermore, the rate of receptor recycling is crucial where it is favorable to have a relatively high returning rate of the receptor back to the surface after internalization [19,20]. This will provide enough high level of receptors available on cell surface for further ligand binding and internalization. Other than internalization, some other receptors found to induce their effect by binding to their therapeutic antagonists (as Z-360), thus concentrating the drug at tumor site to induce their cytotoxic effect without internalization [21]. Such non-internalizing receptors mediated therapy is known to be successful when the targeted receptor is highly expressed on cancer cell and the drug is released from the ligand drug conjugate without the need to internalize the cell, as utilizing the extracellular hydrolytic enzymes (as matrix metalloproteinase 2 (MMP2) and MMP9) in case of solid tumors [22].

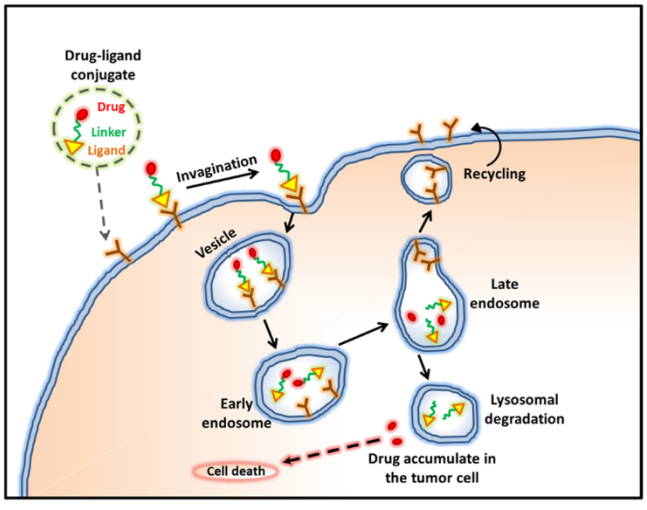

Fig. 1. Schematic representation of receptor mediated ligand-drug conjugate endocytosis. The ligand binds to the receptor expressed on cancer cell surface which stimulates membrane invagation at the site of ligand receptor binding forming a vesicle (early endosome), where the increased vesicular acidity "lowered pH" initiates ligand receptor separation. In the endosomal vesicle, the drug is released from ligand and the receptors are carried back to the cell membrane to be reused for other endocytic cycle.

1.2. Features of ligand selection for Ligand targeted therapy (LTT)

Binding affinity and specificity: Since the ligand in LTT serve to bind both the receptor and the therapeutic drug, the ultimate ligand for LTT on one hand, should have the capability of specifically binding the receptor in high affinity which is favorable to saturate the tumor cells with ligand drug conjugate at lower concentration. On the other hand, the drug should be linked to the ligand strong enough not to be released during its journey to the tumor cells and weak enough to be released inside or in the vicinity of the cancer cells thus allowing drug release in a properly manner and exhibiting appropriate cytotoxic effect [23,24]. In some cases, the selected ligand can bind to other non-tumor specific isoform of the receptor expressed on other normal cells too, resulting in the unwanted toxic effects in healthy tissue. In such cases the solution could be to use a ligand which binds specifically to either the tumor specific isoform of the receptor or binds to the allosteric binding site which differs among different isoforms of a protein [25]. One more advantageous point that could be provided in the ligand is to have a derivatizable functional group (such as a carboxylic acid, amine, alcohol, thiol or halo-aromatic substituent) that facilitates the conjugation of the drug [26,27]. Usually, such binding might interfere with the ligand receptor binding affinity; thus, it has to be investigated.

Ligand drug conjugate: To form the ligand-drug conjugate (LDC) they are bound either directly through functional groups on both the drug and the ligand, or indirectly using a linker designed with certain properties to enhance the LDC efficacy (Fig. 4) [28]. Generally, in order to form the LDC several crucial points should be considered while designing the linkage. Firstly, the resulting size of the whole conjugate that can be adjusted by controlling either the targeting ligand or the linker used [19,29]. Secondly, the linker used should preserve or add several characteristics to the resulting LDC, which would improve its pharmacokinetic properties, as water solubility and serum protein binding [30]. Furthermore, the length of the designed linker is fundamental for the LDC binding affinity to the cellular targeted receptor. Moreover, the stability of the linker is favored at physiological conditions ensuring the LDC efficacy, however linkers are desired to lose their stability (hydrolyzed) at acidic pH as in the endocytic vesicles thus releasing the drug at endocytosis [31–33]. Other methods applied to release the drug from LDC include disulfide bridge reduction and designing a linker with sequence recognized by the lysosomal enzymes hence hydrolyzed by the endosomal/lysosomal enzymes [34–36]. Thirdly, the selection of a proper drug is pivotal in LTT giving rise to the desired cytotoxic effect of tumor cells. Such drugs should be highly potent and easily released after cleavage from endosomal capsule [37].

2. Mode of targeting

As previously mentioned, in general there are two approaches to target the cancer tissue or cells, 1) either passive targeting where the changes in the structural features of the tumor vasculature are governing its uptake, or 2) the active targeting (Fig. 2). Tumor cells are known to release factors that induce the formation of new vessels (angiogenesis) to ensure tumor supply with nutrients. This results in vast irregularity in structure allowing the penetration of relatively large molecules through the blood-tissue barrier, hence accumulation in the tumor tissue. This phenomenon as defined by Y. Matsumura and H.A. Maeda is known as the Enhanced Permeability and Retention effect (EPR effect) [38] (see reviews [39,40]. Passive tumor targeting utilizing the EPR effect has been successfully applied in solid tumors and many of the passive targeting nano-carriers approved by FDA (Table 2). However, passive targeting therapy had several drawbacks such as variation in the tumor endothelium overall permeability affecting the uptake of macromolecules as antibodies and the decreased concentration of tumor antibody compared with plasma concentration, in addition to unwanted general

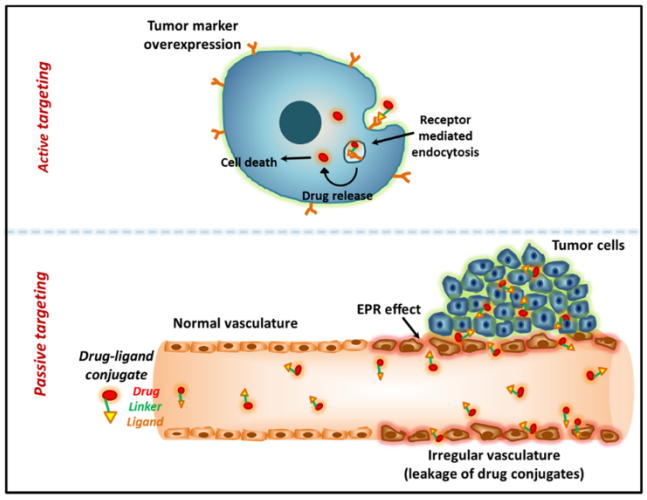

Fig. 2. Schematic illustration of different targeting modes in targeted cancer therapy. Passive Targeting *"Lower panel"*, due to the malignant transformation, the endothelial lining of the vessels is disrupted and the basement membrane integrity is lost. This results in Enhanced Permeability and Retention effect "EPR" where an aberrant leakage of some molecules into the surrounding cancer tissue takes place, allowing the access of the targeted drug and cancer cell death. Whereas Active Targeting *"Upper panel"*, requires ligand bound drug to be carried to the cancer cell via a specific binding of ligand to its receptor on tumor cells. The internalized receptor-ligand-drug complex is dissociated by the effect of acidic endosomal environment, releasing the drug into the cancer cell developing the cytotoxic effect "cell death".

toxicity upon treatment of metastasis and circulating cancer cells [39, 41]. Another means of targeting is the active targeting which is applied in the LTT. The mode of active targeting is based on the previously mentioned "magic bullet theory", which involves a cancer cell specific marker targeted by other specifically binding molecules (as ligands). The targeting molecules are linked to the anti-tumor agent (drug) and consequently this will result in the drug accumulation at the vicinity of tumor cells [3]. The variety of targets on tumor cells has been increased lately; many of these markers are known to play a crucial role in tumor metastasis, migration, angiogenesis and invasion, thus found to be either low or non-expressed by the normal non-tumor cells. Examples include, cancer specific receptors (epidermal growth factor receptor family "EGFR", vascular endothelial growth factor receptors "VEGFR" and transferrin receptors "TfR") and cancer specific antigens (B-cell maturation antigen "BCMA", clusters of differentiation "CD19" and prostate-specific membrane antigen "PSMA"). The targeting molecules have been expanded recently depending on the targeted cancer cell marker and this includes ligands for receptors known to be highly expressed on the surface of cancer cells, such as antibodies and their recombinant derivatives, in addition to peptides which can be either cell penetrating peptides or tumor homing peptides (Fig. 3). In the following section, some examples of the three classes of targeting molecules will be discussed.

2.1. Antibody mediated targeting

The emerge of hybridoma method allowed the development of solutions using monoclonal antibodies in therapies. In targeted therapy, monoclonal antibodies can be used either alone to label cancer cells for immune system mediated cytotoxicity (either complement dependent or antibody-dependent cellular cytotoxicity), or the monoclonal antibodies

Table 2
Examples of some FDA approved nano-carriers exploited in targeted and non-targeted therapies.

Nanoparticles	Drug		Type of cancer	Ref.
Liposomal anti-tumor drugs.	liposomal form of doxorubicin	Doxil®(ALZA corp., Mountain View, CA, USA), Caelyx (Doxil)® (Janssen Inc., Toronto, Canada) Myocet® (Teva B.V., Haarlem, The Netherlands))	Ovarian and breast cancer, multiple myeloma and Kaposi's sarcoma	[212,213]
	Liposomal form of daunorubicin	DaunoXome® (Galen Ltd., Craigavon, UK))	HIV-associated Kaposi's sarcoma	[214]
	Liposomal form of cytarabine	Depocyt® (Pacira Pharmaceuticals, Inc., San Diego,CA, USA))	neoplastic meningitis	[215,216]
	Liposomal form of mifamurtide	Mepact® (Takeda Pharmaceutical Co. Ltd., Tokyo, Japan))	high-grade, resectable, non-metastatic osteosarcoma	
	Liposomal form of vincristine	Marqibo® (Spectrum Pharmaceuticals, Inc., Henderson, NV, USA))	acute lymphoblastic leukemia	
	Liposomal form of irinotecan	Onivyde®Merrimack Pharmaceuticals, Inc., Cambridge, MA, USA)	metastatic pancreatic adenocarcinoma	
albumin nanoparticles	Albumin nanoparticles loaded with paclitaxel.	Abraxane® (Celegene Corporation, Summit, NJ, USA)	metastatic breast cancer, non-small cell lung carcinoma, pancreatic cancer, cervical cancer	[217,218]
	Albumin nanoparticles loaded with lapatinib.		triple negative breast cancer and HER2-positive breast cancer	[219]
	albumin nanoparticles loaded with gemcitabine		pancreatic cancer	[220]
	albumin nanoparticles loaded with siRNAs		breast and lung cancers	[221]
Organic polymer particles	Synthetic polymers	polyethylene glycol polylactic and polyglycolic acids polycaprolactone derivatives of polymethacrilic acid	Solid tumors as breast cancer.	[222–225]
	natural polymers	gelatin chitosan dextran	Breast cancer	[2226–228]

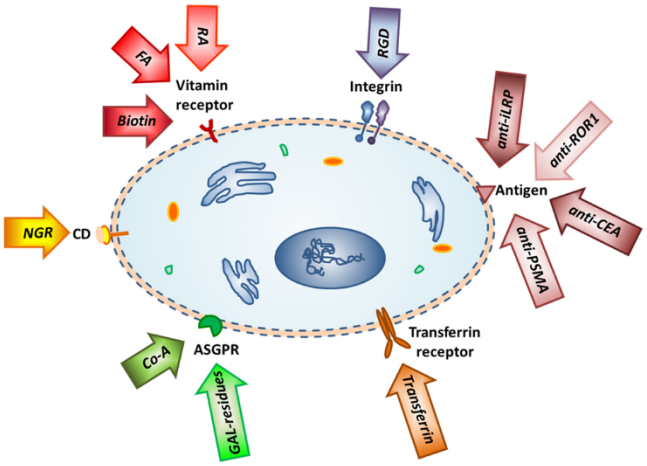

Fig. 3. Summary of some markers over-expressed in cancer cells and their ligands for targeted cancer therapy. ***CD***: cluster of differentiation; ***NGR***: a tri-peptide asparagine-glycine-arginine; ***FA***: folic acid; ***RA***: retinoic acid; ***RGD***: a tri-peptide arginine-glycine-asparagine; ***iLRP***: immature laminin receptor protein; ***ROR1***: receptor tyrosine kinase-like orphan receptor 1; ***CEA***: carcinoembryonic antigen; ***PSMA***: prostate specific membrane antigen; ***ASGPR***: asialoglycoprotein receptor; ***GAL***: glycolsylated; ***Co-A***: concanavalin-A.

used as carriers for the anticancer drug specifically to the tumor cells. Here, the antibody is conjugated to cytotoxic drug by a stable linker and this complex binds to the antigen on cancer cells. Despite its high selectivity, this type of therapy had some limitations that lower its effectiveness, such as varying expression of tumor specific antigen, and varying antibody-drug complex binding affinity [4]. Some of these ADCs are authorized by the FDA as Ado-trastuzumab emtasine (Kadcyla) directed against Her-2 positive breast cancers, and brenduximab vedotin (Adcetris) which specifically targets CD30 antigen which is a marker for Hodgkin lymphoma and systemic anaplastic large cell lymphoma [42,43].

Another approach exploited is the enzymatic prodrug activation carried to the tumor by the specificity of monoclonal antibody, known as antibody directed enzyme prodrug therapy (ADEPT) [44]. We recently, carried out work which overcome the main pitfalls of this therapy and could lead to major improvement in such therapy [45–48]. The ADEPT is carried out on two steps (Fig. 4). As the first step of ADEPT is the administration of the enzyme-prodrug complex into the system to allow the complex to bind to antibody specific antigen "tumor specific marker", the rest of unbound complex is cleared from the system. This is followed by injecting of the prodrug. This circulating prodrug is safe and inactive until it reaches the site of tumor where the antibody-enzyme complex is bound. The enzyme acts on and activates the prodrug to a potent cytotoxic drug resulting in killing tumor cells. Several antibodies or molecules (peptides) have been conjugated with enzymes to be used in ADEPT [49].

Tumor cells are known to express diverse groups of antigens that can be targeted to distinguish cancer cell population. In ADEPT such antigen should have the previously mentioned properties required for targeted therapy as to be a cell surface protein (i.e., can be reached from the blood stream), and specific to the tumor cell. There have been several antibodies designed to target such antigens, in this review we will deal with some of the common ones.

2.2. Prostate specific membrane antigen

Prostate specific membrane antigen (PSMA) is a membranous glycoprotein normally expressed by cells of several normal tissues in addition to the prostate, such as small intestine, salivary gland and renal tubules [50,51]. PSMA was originally found to be highly expressed in prostate cancer cells, however several recent studies confirmed its high

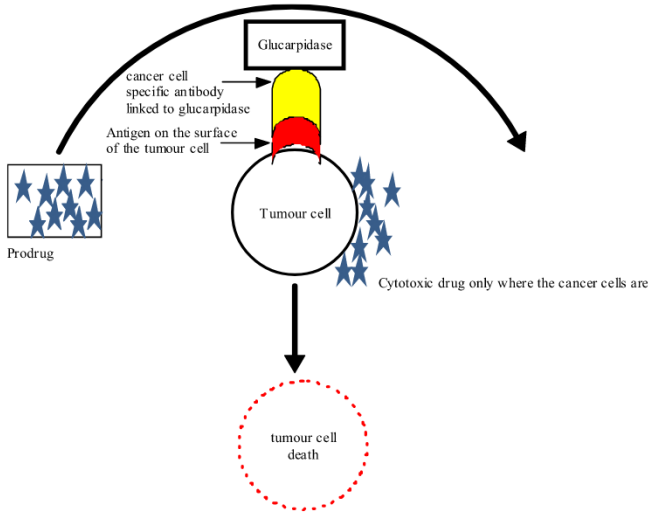

Fig. 4. The principle of ADEPT. In the first phase, an antibody enzyme fusion protein is injected i.v., and allowed to localize to tumors. After clearance of conjugate from circulation, a prodrug is given in the second phase. The enzyme cleaves the prodrug to release the active drug. The extracellularly generated drug can diffuse throughout the tumor and kill antigen positive tumor cells as well as tumor cells not expressing the relevant antigen, thus giving a "bystander'' effect [229].

expression in neo vasculature of many other solid tumors [50,52], indicating important role of PSMA in the tumor angiogenesis [53,54]. Studies indicated some functions of this membranous protein as its folate hydrolysis activity or neuropeptidase type function [55]. Since PSMA was found to have crucial role in angiogenesis, tumors were targeted by anti-PSMA antibodies for cancer therapy. Such therapy was found to be selective and would spare normal tissue either expressing or not expressing PMSA, as in intestinal cells Abs suffer from difficult accessibility to the luminal side of the intestinal epithelium. In addition, because of the large size of Abs their filtration to the glomeruli is prevented [56].

Furthermore, PSMA expression level was used as indicator of the tumor grade for prostate cancer and brain gliomas [57]. A recent study employed the high expression of PSMA in prostate cancer to selectively target the tumor with an anti-cancer drug enterolactone (EL), hence avoiding the unfavorable side effects and enhancing its effectiveness in prostate cancer. The anti-PMSA Ab (D7) was conjugated with the enzyme β-glucuronidase (βG) giving the fused enzyme-Ab complex (D7-βG). The enzymatic activity of the enzyme to activate enterolactone-glucoronic acid conjugates (EL-Glu) into the EL was tested. The results showed to be promising when applied in-vitro and in vivo for examination of the restricted EL-Glu activation at the site of PSMA highly expressing tumors [58]. Moreover, Luo et al. employed the prostate-specific membrane antigen (PSMA) targeting ligand and conjugated it with optimized gold nanoparticles (AuNPs) for targeted X-ray radio therapy [59].

2.3. Drug Delivery using gold nanoparticles

The advance in nanotechnology lead to the production of numerous nanoparticles made from many elements such as gold, silver, cobalt, platinum, iron, copper and many others. These nanoparticles have been synthesized either biologically or physiochemically [60].

The implementation of nanotechnology in cancer research has significantly, progressed the field of cancer diagnosis and treatment. Two of the important area nanotechnologies helped the progress of cancer treatment are controlling the drug release withing tumoral immune microenvironment and reversing the drug resistance [61,62].

Nanoparticles has been used as bio-vehicles to deliver nanovaccines

which has been proven as an effective delivery system capable to trigger the antitumor immunity [63–65]. The design of nanoparticles to deliver nanovaccine has been discussed in a leading review by Pere Santamaria and colleagues [66].

In a recent review, Moore and Chow [67] discussed the recent progress and applications of gold nanotechnology in medical biophysics using artificial intelligence and mathematical modeling. In their review they discussed that gold nanoparticles have benefited multimodal cancer therapy. This was achieved due to the ability of gold nanoparticles to produce cytotoxic reactive oxygen species (ROS) they can also be applied within photo-thermal and sono-dynamic therapy (SDT), respectively [67,68].

In another recently published review [67,69], the authors provided a comprehensive discussion on how the surface coating of gold nanoparticles with accurate control of particle size, shape and surface chemistry were improved by the advance of synthetic technique. These provide a very efficient gold nanoparticles which are much safer and easier drug to apply to the cancer patients.

Siddique and Chow have found [70], in their review comprehensive article, that the future development in cancer therapy and medical imagine will be enhanced by synthesis and design of novel nanomaterials. They also concluded [70] that side effects and cell toxicity of nanoparticles should be carefully examine and more resources should be available to achieve this aim.

Finally, nanoparticles play a very important part in medical imagine and in modern cancer therapy. They can deliver many drugs to targets sites other bio-vehicles cannot reach. The nanoparticles success in cancer therapy so far will significantly affect the funding and the future research on cancer therapy and medical imaging[70].

2.4. Oncofetal antigen

Oncofetal antigens are a group of proteins normally expressed in early fetal developmental phase and suppressed in the adult tissues. Their genes become abnormally activated in tumors due to various reasons as epigenetic changes or by viral antigens induced mutations [71]. Several oncofetal antigens have been identified in various tumors, investigated and employed in cancer therapy. A commonly studied classical oncofetal antigen is the carcinoembryonic antigen (CEA), which name was derived from the fact that it was first identified to be expressed either in cancer or embryonic tissues. CEA is a glycoprotein and is one of the most widely used cancer markers globally. It has been used mainly in gastrointestinal cancers, especially in colorectal malignancy.

Normally CEA is highly expressed by fetal gastrointestinal tissue, which is silenced later at birth. Abnormally elevated CEA levels were found in the serum of some type of cancers, mostly gastrointestinal cancers as colorectal malignancies, thus considered one of the frequently used tumor marker worldwide [72]. The only problem with such tumor marker is the circulation of soluble antigen, which makes targeting tumor cells hard. However, several early studies employed CEA to target the tumor cells and tried to seize this problem [73]. An antibody against CEA was conjugated with the enzyme CPG2 that is required for the activity of prodrug (CMDA), but early investigations found non-selective activation of the prodrug in circulation. This is due to the release of the enzyme from the Ab-Enz conjugate or the circulating Ab-Enz in the blood. To overcome this problem an antibody developed to bind and inactivate the circulating enzyme CPG2 (SB43). Furthermore, this Ab was glycosylated (SB43-Gal) to achieve fast clearance by liver and to avoid the inactivation of the Ab-Enz at the site of tumor [74]. Applying such approach was very successful when the animal with colon cancer was injected with Ab-Enz complex first, followed by the clearing glycosylated Ab. Once the free AB-Enz is cleared, the prodrug administration takes place as the third step of the therapy(Fig. 5) The clearance of the free enzyme or the AB-Enz conjugates before the administration of the prodrug reduced significantly the side effect of the therapy [75].

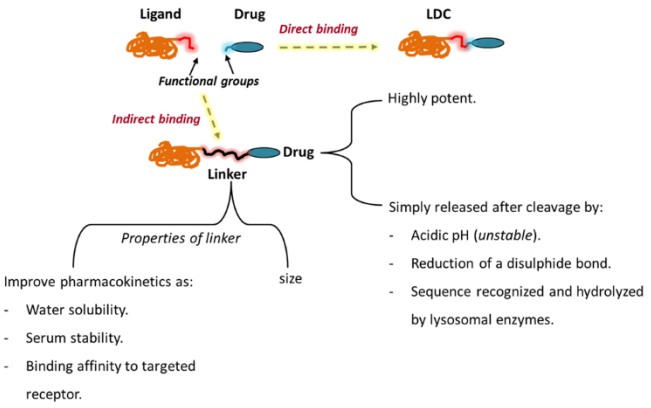

Fig. 5. Schematic summary of the main properties of linker and drug forming the ligand drug conjugate (LDC).

Receptor tyrosine kinase-like orphan receptor 1 (ROR1) is another oncofetal protein known to be highly expressed during embryogenesis required for skeletal and neuronal development. After birth very low levels of ROR1 are found normally in some tissues as adipose tissue, parathyroid and some tissues of the gastrointestinal tract [76]. Higher abnormal levels of ROR1 were found in many hematological malignancies as chronic lymphocytic leukemia, which were found to play an important role in tumorigenesis and cell migration [77,78]. Several studies used ROR1 antigen to target tumors and the efficacy of ROR1 specific monoclonal antibodies, chimeric antigen receptor T cells, siRNA and tyrosine kinase inhibitors were investigated. This was thoroughly reviewed recently by Shabani et al. discussing latest studies employing ROR1 for selective cancer immunotherapy, suggesting ROR1 an ideal marker to be targeted for cancer immunotherapy with high selectivity and least side effects [79].

Immature Laminin receptor protein is an oncofetal antigen referred as iLRP or OFA/iLRP was first found or recognized by Coggin et al. to be highly expressed at the early embryonic stages, which as other oncofetal proteins lowered or stopped in the following birth phase [80]. Furthermore, Coggin and his colleagues found that various tumors abnormally express high levels of the antigen (iLRP), which extensively affected tumor growth and metastasis [81,82]. As an immune response to this antigen, Auto-antibodies were found in the serum of leukemia patients highly expressing iLRP, and such anti- iLRP Abs demonstrated cytotoxicity to the iLRP positive tumor cell lines [83]. Another study confirmed the efficacy of anti- iLRP Abs on cancer therapy. The results on two tumor models (A20 B-cell leukemia model and the B16 melanoma model) indicated remarkable selective efficacy in suppressing tumor formation [84]. A recent study employed targeting acute myeloid leukemia (AML) by selective delivery of chemotherapy (Dox) to the AML cancer cells highly expressing iLRP using an aptamer (AB3) for iLRP [85].

2.5. Peptide mediated targeting

2.5.1. Amino peptidase N (CD13)

One of the approaches to target tumor cells is to use a small peptide motif known to selectively bind to an epitope highly expressed on tumor cells. For cancer cell metastasis and angiogenesis, aminopeptidase N (APN) was found to be highly expressed on tumor cells thus represents a favorable binding site to target cancer cell death [86]. A range of different cancers showed to express aberrant high APN levels, thus employed as cancer markers adding into clinical outcomes prediction, in addition to targeting APN on tumor cells for treatment as in malignant pleural mesothelioma, small cell lung cancer and breast cancer [87–89].

It has been shown that a small cyclic peptide asparagine-glycine-arginine (CNGRC) can bind with high affinity to cells highly

expressing APN. The peptide Therefore, serves as an ideal candidate for tumor imaging and detection. The peptide also could be used in targeting cancer therapy to deliver an enzyme or toxic drug to the tumor highly expressing APN [90–94]. Several recent studies successfully generated CNGRC fused protein conjugates to be implemented in ADEPT such as CNGRC fusion with the enzyme cytosine deaminase [95] or Carboxypeptidase G2 [96]. Such fusion proteins showed promising results in vitro with APN expressing cells, demonstrating selective higher binding and cytotoxic effect in high APN expressing cell lines. Moreover, Shao et al. employed embolization therapy and designed a peptide asparagine-glycine-arginine (NGR) labeled thrombus construct. Interestingly their results showed tumor neo vessels heavily loaded with the constructs associated with increase tumor cells apoptosis and inhibition [97]. In another approach to target CD13 highly expressing tumor cells, NGR tripeptide was conjugated with the anti-cancer drug Daunorubicin to be carried to the cancer cell site. NGR-Dau-conjugates showed a remarkable antiangiogenic effect in addition to a significant inhibition of tumor cells proliferation [98].

Furthermore, the arginine-glycine-aspartic acid (RGD) and asparagine-glycine-arginine (NGR) peptide were used in conjunction with anti-inflammatory drugs naproxen and ibuprofen. The conjugates exhibited better activity compared to the non-conjugated drugs, and showed enhanced binding to tumor cell lines expressing their receptors [99]. Since Aminopeptidase N is known for its important role in enhancing angiogenesis, it has been targeted by non-peptide molecules which bind to the active site of APN and block and/or inhibit its activity. Antibodies as anti-CD13 used for acute Myeloid leukemia therapy, or inhibited by Ubenimex (Bestatin) which found to induce cancer cell death through its binding to CD13 [100,101]. Moreover, various studies employed the high cancer cell expression of APN in imaging and quantitative profiling which proved to have a high impact on targeted therapeutic efficacy evaluation and better cancer diagnosis [91,102,103].

2.6. Integrin αvβ3

Integrin receptors on the cell surface are important for the cell adhesion, migration and angiogenesis. High expression of integrin αvβ3 has been associated with some types of tumor cells and vascular endothelial cells [104]. A tri-peptide asparagine-glycine-arginine (RGD) motif is known to bind selectively to αvβ3 integrin receptor. Such binding was shown to inhibit angiogenesis. Furthermore, it has been used to target tumor cells with an anticancer drug or prodrug activating enzyme [105,106]. Jiang et al. successfully proved the efficiency of using RGD in delivering the anti-cancer drug to the tumor site and thus resulting in a significant tumor cell cytotoxicity [107]. Moreover, modified RGD-liposomes co-loaded with paclitaxel and curcumin showed remarkable anti-tumor effect compared with the non-RGD modified ones. Another form of RGD was discovered by Sugahara et al. known as iRGD (internalizing RGD), which found to have higher efficiency in tumor cell penetration [108]. This form of RGD was investigated by several studies utilizing iRGD in targeted cancer therapy and well-reviewed recently by Yin et al. [109]. Most of these studies used iRGD as a transporter for the anti-cancer drug such as doxorubicin loaded liposomes, or paclitaxel to be delivered to the tumor site and to penetrate to the tumor cell. Most of these studies confirmed cellular uptake of these drugs and resulting in notable tumor growth inhibition with less system toxicity [110,111]. Likewise, a recent study on RGD targeting for co-delivery of doxorubicin (DOX) and the natural product betulinic acid (BA) showed that the resulting complex induced better anti-tumor therapeutic effect on ovarian cancer cell line Skvo3 with lower cardiotoxicity [112].

2.7. Receptor mediated targeting

2.7.1. Folate receptor

Folate receptors are highly expressed in several malignancies as ovary, kidney, lung, brain, endometrium and breast cancer [113]. Folate directed enzyme prodrug therapy (FDEPT) was illustrated by Zhang et al. several years ago where folate labeled enzyme (penicillin-G amidase) was made and showed to hydrolyze the prodrug N-(phenylacetyl) doxorubicin to a cytotoxic drug [114]. In vitro and in vivo studies demonstrated higher toxic action with better selectivity to the folate receptor positive cancer cells. Furthermore, the results showed better drug clearance from the blood system and an improved cellular drug uptake. Another approach to target folate receptors was to use lysosome encapsulated drug (pegylated liposomal doxorubicin) directed via folate conjugation to the folate receptors on tumor cells [115]. The results exhibited significantly improved effect of the drug compared with free doxorubicin. Folate has been extensively used in conjugation with several other drugs to form therapeutic nanoparticles targeting cancer cells, such as Paclitaxel and methotrexate [116,117]. In addition to the chemotherapeutic drug, a therapeutic micelle was formed by conjugation of folate with meta-tetra (hydroxyphenyl) chlorine (a photosensitive substance), thus selectively damaging tumor cells upon photodynamic therapy [118]. Another example of combined cancer targeted therapy was recently published by Zhang et al. who presented designed nanoparticles employing photothermal and chemotherapy [119]. These nanoparticles were composed of pH reduced dual responsive and folate with polymeric micelles encapsulating doxorubicin (DOX) and indocyanine green (ICG) for imaging and photo-thermal therapy purposes. Such nano-particles were tested in vitro and in vivo on human hepato-cellular carcinoma cells (BEL-7404) and found to result in a remarkable targeting to folate receptors on tumor cells and effective tumor growth suppression. Reduced pH triggered Dox release, which results in cytotoxic cell death, in addition to hyperthermia as a result of laser irradiation based ICG triggering. Both the chemo and the photothermal therapy proved to reduce tumor size effectively. Dendrimer nanoparticles are synthetic growing polymers that have been employed in cancer therapy. A recent review highlighted the use of folate receptor targeted delivery of chemotherapeutic drug and human antigen R (HuR)-targeted siRNA into dendrimer nanoparticles [120].

2.7.2. Somatostatin receptor

Somatostatin receptors are G-protein coupled receptors highly expressed in a variety of cancer cells as colon, kidney, brain tumors (menengiomas and glioblastomas) and endometrial tumors. The high expression of somatostatin receptors served as a promising target to induce cancer cell death [121]. The ligand of Somatostatin receptors, somatostatin is neuro-peptide mainly found in nervous system beside other tissues as lungs, bone and thyroid gland [122]. Somatostatin is known for its anti-proliferative, pro-apoptotic effect on cells upon binding to its somatostatin receptor, thus enhancing cell death [123]. This initiated somatostatin utilization as an anti-cancer agent, but due to its short half-life, several analogous of somatostatin with prolonged half-life have been developed targeting highly expressed somatostatin receptors on cancer cells. Such analogous were radio-labeled for the radionuclide therapy, aiming to be targeted to the somatostatin receptor highly expressing tumors [124]. Furthermore, somatostatin and its receptors have been effectively used in cancer imaging and therapy [125]. Several pre-clinical studies compared differentially radionuclide labeled somatostatin analogs, as [^{90}Y]-DOTA,Tyr[3]]octreotide, [111In]-DTPA]octreotide and [177Lu]-DOTA,Tyr[3]]octreotate. The radiolabeled [177Lu]-DOTA,Tyr[3]]octreotate showed highest tumor uptake of all tested octreotide analogs by the somatostatin receptor subtype 2 expressing tumor cells. Moreover, they indicated the favorable effect of combining differentially radiolabeled somatostatin analogs like 90Y and 177Lu on tumor size suppression [126]. Furthermore, many studies showed the development of therapeutics of chemotherapeutic agents conjugated to a somatostatin analog, thus directing the cytotoxic drug to the tumors highly expressing

somatostatin receptor [127].

A recent study employed somatostatin analogs specific for somatostatin receptor 2 known to be highly expressed in breast cancers. The synthetic analog was successfully conjugated to liposome nano-particles filled with a chemotherapeutic drug Diacerin. The results on breast cancer cell lines (in vitro) and MDA-MB231 tumor xenografted models showed remarkable cytotoxic effect on the tumor with enhanced efficacy (Bharti et al., 2017). Following a similar concept, Nguyen et al. prepared other targeting nano-particles composed of the somatostatin analog (Lanreotide) with two types of anticancer therapeutics: chemical drug methotrexate and the photosensitive substance polyaniline. They found significant cytotoxic effect on variety of cancer cells [128].

In recent studies investigators succeeded to develop a therapeutic conjugate of Technetium-99 m (^{99}mTc) and Rhenium-186 (186Re) with somatostatin receptor antagonist, and established their high concentration in neuroendocrine tumor (NET)cells highly expressing somatostatin receptor in vitro and in vivo mouse models [129,130]. [^{177}Lu] Dotatate is another somatostatin receptor specific dionuclide labeld peptide, has been approved by FDA in January 2018 and the first radiopharmaceutical for peptide receptor radionuclide therapy to treat gastroenteropancreatic NET [131,132].

2.7.3. Transferrin receptor

CD71 which is known as transferring receptor 1, is highly expressed on tumor cells and it can be used as an indication for the stage of malignancy [133,134]. Upon transferring binding to its receptor, the ligand-receptor complex is internalized into the cell by endocytosis and the cargo is released in the cell by the lowered pH, which makes it a promising target for the delivery of anti-cancer compounds and genes in to tumor cells [135]. Targeting transferrin receptor 1 for cancer therapy has been facing many limitations as competitive binding to the receptor with the native systematic transferrin (normally expressed on cells), thus interfering in the binding of therapeutic transferring analogs resulting in its lower cytotoxic effect. In addition to the normal tissue toxicity due to the non-specific binding to the other isoforms of transferring receptors expressed on normal tissue as hepatocytes [136]. to evade such drawbacks, two major approaches employed to target transferring receptors. One approach is targeting with transferrin antagonists as monoclonal antibodies 42/6 and A24 [137,138], thus inhibiting their activity. A second approach is targeting with therapeutic agents to be taken up by tumor cells. Several therapeutics have been linked to transferrin or its analog in a nano-particles. Chemotherapeutics as Doxorubicin proved to inhibit multidrug resistance and to lower the non-specific toxicity of normal cells, plant and bacterial toxins Ricin, mutant diphtheria toxin and nucleases (ribonuclease) [139–141]. Furthermore, transferrin was conjugated with nucleic acid, which is known as transfer infection i.e targeting tumor cells with genes to enhance apoptosis and cell death as with TNFα and p53 genes [142,143]. A recent study by Deshpande et al. combined transferrin receptor targeting with another tumor targeting method, arginine-rich cell penetrating peptides as the octa-arginine "R8" [144]. DOXIL "Doxorubicin encapsulated PEGylated liposomes" was enhanced with two targeting molecules, transferring and R8. The results showed impressive therapeutic efficacy where the drug (Dox) targeted to tumor cell by transferrin, and R8 mediated the intracellular delivery. Similarly, Tan et al. used modified Cisplatin prodrug nano-particles labeled with dual targeting factors, transferrin and folate. The cytotoxic effect of the constructed nanoparticles was highly significant on tumor cells [145,146].

Thyroid cancer therapy with Sorafenib (kinase inhibitor) suffers from non-specific toxicity resulting in serious side effects, thus Ke et al. utilized high transferrin expression in cancer cells to develop nano-particles of transferrin as a carrier of the drug (Sorafenib) for targeted delivery [147]. Their findings established higher uptake by transferring receptor expressing cancer cells indicating selective cancer cell toxicity. In the same context, several others used transferrin receptor targeted nanoparticles loaded with chemotherapeutic drugs for therapy, as directed to the transferrin receptor expressing blood brain barrier cells to treat cerebral infarction, the hepatocellular carcinoma, or selective delivery of siRNA to the tumor cells which found to enhance its stability too [147–151].

2.7.4. Asialoglycoprotein receptor

Lectins (carbohydrates binding proteins) have been engaged lately with targeted cancer therapy known as Lectin-directed enzyme-activated prodrug therapy (LEAPT). Some of these lectins were found to be highly displayed on surface of tumor cells, thus used as targets for therapeutic agents [152]. In LEAPT, lectins have been utilized in combination with the constructed glycosylated enzymes and prodrugs. One of the mostly exploited lectin in the targeted therapy is asialoglycoprotein receptor (ASGP-R). Glycoprotein serum clearance studies showed that ASGP-R is highly expressed on the surface of liver cells and have been targeted with many molecules as glycosylated therapeutic drugs and glycolsylated enzymes [153,154]. In LEAPT firstly the engineered glycosylated-enzyme is specifically delivered to the cells, and the enzyme internalizes to the cells by endocytosis. Secondly, the synthetically capped prodrug is administered and once taken up by the cells, the enzyme hydrolyzes and activates the prodrug into cytotoxic drug. To make such process more tumor specific the capping molecules (α-L-rhamnoside) and the hydrolytic enzyme (α-rhamnosidase) selected would be of non-mammalian origin thus ensuring prodrug inactivity except at the site of tumor [155]. Garnier et al. and others used a similar system to develop glycosylated prodrugs of doxorubicin and 5-fluorouracil capped with the sugar L-rhamnoside. The prepared compounds were tested for application in LEAPT, and the results were remarkably effective on liver cancer cells and were as expected, proving the possibility to use variety of drugs in LEAPT [155,156]. Another approach recently used was utilizing magnetic nano-particles to target high ASGP-R expressing tumors (as hepatocellular carcinomas). In this study, Xue et al. engineered galactosylated-carboxymethyl chitosan-magnetic iron oxide nanoparticles (Gal-CMCS-Fe_3O_4-NPs), and tested their distribution following application of external magnetic field. They found NPs highly concentrated in hepatocytes proving their ASGP-R mediated selectivity. Furthermore, the constructed NPs were conjugated with the tumor suppressor gene Ras Association Domain Family 1 A to be transfected into tumor cells. Their results demonstrated enhanced tumor cell death and reduced tumor size, thus supporting successful use of ASGP-R in a gene therapy system [157]. Plant lectins have been widely used in the designing and production of ASGP-R targeted nano-carriers that can deliver therapeutic drugs specifically to the tumor cells. This have been extensively reviewed by Bhutia et al. who showed their potential clinical applications and findings for their capability towards efficient binding to cell markers thus targeting the cancer cells [158]. Angelica sinensis polysaccharide is one of the utilized plant lectins lately, that binds ASGP-R. and the produced nanoparticles carry the drug to tumor site as hepatoma cells [159]. Concanavalin-A is another plant polysaccharide that have been exploited to produce Concanavalin-A conjugated nanotransfersomal gel used with UVB induced skin carcinoma. The conjugates found to produce higher toxicity towards melanoma cells compared with the normal skin cells [160].

The drug carriers and cancer specific receptor discussed in this report are shown in Fig. 7.

2.8. Drug delivery and targeting cancer cells using polyethylene glycol conjugation

We reported above possible drug delivery using cancer specific antibody or cancer specific receptor peptides. It was also reported that the drug delivery to cancer could be improved using Polyethylene glycol (PEG). It has been shown that PEG in combination with niosomes i.e. non-ionic surfactant-based vesicles can carry various drugs within them, to improve cell targeting[161] as shown in Fig. 6.

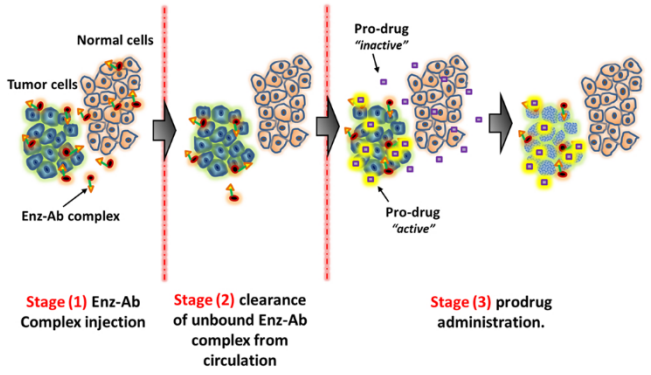

Fig. 6. Scheme of three stages antibody directed enzyme pro-drug therapy (ADEPT)of tumor cells. At stage [1] the enzyme antibody complex. (Enz-Ab complex) injected in the body which travels in the circulation and binds to antibody specific cancer marker on the surface of tumor cells. Followed by stage [2] where the un-bound Enz-Ab complex would be cleared from circulation. At stage [3] a pro-drug (inactive form of the drug) administered into the body and once reach the tumor site become activated to highly cytotoxic drug by the action of enzyme at tumor cells site.

3. Advantages, limitations and critical analysis of targeted cancer therapies

The development of agents for targeted cancer therapy has changed the game in cancer treatment and overcome many of the pitfalls of the traditional cancer therapy such as chemotherapy and radiotherapy. Targeted cancer therapy has increased significantly the overall survivals of patients with many cancer diseases which, traditionally have very poor prognosis such as chronic myeloid leukemia, renal cell carcinoma [162–165].

Targeted therapies, however, have some limitations and disadvantages. The hardest obstacle to targeted cancer therapy is the inevitable occurrence of drug resistance Figs. 7 and 8.

Targeted cancer therapy is based on the assumption that targets for cancer cells are unique and specific but, in most cases, there is a cross reactivity between targets on cancer cells and normal cells. This cross reactivities leads to a great deal of toxicity in other organs where they share the targets.

GI and gut epithelial cells express EGFR. Administration of EGFR targeting drugs against cancer cells will not only targets EGFR-expressing cancer cells but also cells within the GI and oral mucosae. This will lead to GI toxicity of EGFR-targeting drugs [162,166]. In some other cases, there are Her-2 neu receptors on heart muscle and also same receptor is associated with breast cancer. Treatment therefore, of Her-2 neu associated breast cancer with targeted drug may lead to cardiotoxicity [167]. There are many other mechanisms which cancer cells eventually resist the targeted drug [168–171].

3.1. Future prospects of cancer therapy

Cancer is a dynamic disease which progress by time to be more heterogeneous. This heterogeneously of cancer cells leads to different level of sensitivity to targeted therapy treatment and eventually to total drug resistance to the traditional therapies including targeted cancer drugs [172].

The recently discovered, the clustered regular interspaced short palindromic repeats system [173,174] (CRISPR) is a novel technique for mammalian cells genome editing based on archaeal and bacteria antiviral defenses systems. Due to its exceptional potential and efficacy, the technique presents a new era in disease treatments including cancer. The discovery of CRISPR will direct the cancer treatment compass to genetic manipulation of the tumor and immune cells instead of inhibiting a certain cancer receptor or protein [175–178].

On the other hand, another approach which will be the focus of the research in the coming years, mRNA vaccine. The recent covid-19-coronavirus -vaccine has been the start of the widespread use of mRNA technology [179,180]. Since the successful mRNA vaccine for Covid-19 the mRNA vaccines have become a promising platform for cancer immunotherapy.

Over twenty mRNA-based immunotherapies are in clinical trials for solid tumor treatment with some encouraging outcome. We believe that the mRNA vaccine for cancer treatment will attract wide spread interest and might overcome many of the disadvantages of the traditional targeted cancer therapy [181–183].

Despite the recent advances in cancer research the recure of tumor and he tumor resistance to drugs remain an obstacle for cancer cure. Studies have shown that small part of cancer cells known as cancer stem cells (CSC) are the main culprit for reconstitution and propagation of the tumor [184–186]. They have the ability to differentiate and proliferate like normal stem cells. One of the future promising approaches for targeted cancer therapies aims for targeting CSCs to overcome possible reoccurrence of tumor and to increase the opportunity of cancer cure.

Finally, the above three approaches for cancer therapy are some of future strategies to overcome the disadvantages of targeted cancer therapy mainly cancer drug resistance and cancer recurrence.

4. Conclusion

The field of exploring and investigating newly discovered cancer markers has been expanding lately and exploited to be utilized in targeting cancer therapy. Ligand and other carrier targeted cancer therapy are an effective approach to deliver a cytotoxic drug to the targeted tumor, therefore improving therapeutic efficacy and lowering the other non-specific cytotoxic side effects. As we reviewed, several methods enhanced the therapeutic properties of the ligand-drug conjugate by defined ligand selection, proper drug use, and engineering a suitable linker. Such methods enhanced favorable physical properties, in addition to preserving ligand binding affinity and drug activity. Since some

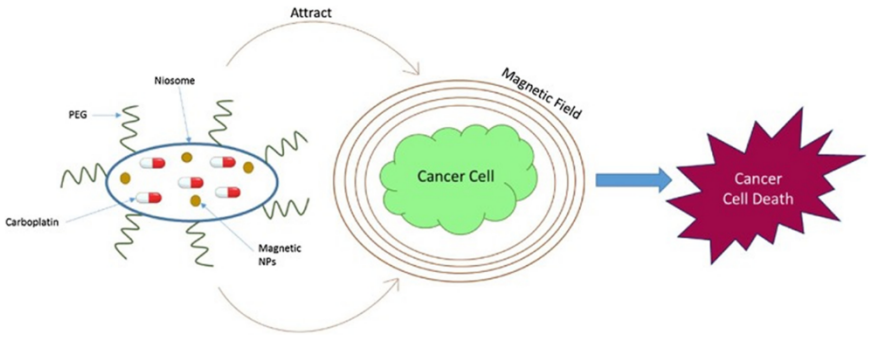

Fig. 7. Use of PEG-coated noisome magnetic nanoparticles to deliver carboplatin to tumor cells. PEG could be used to increase locally the drug concentration in the vicinity the tumor by using external magnetic field, for more details see [161,230].

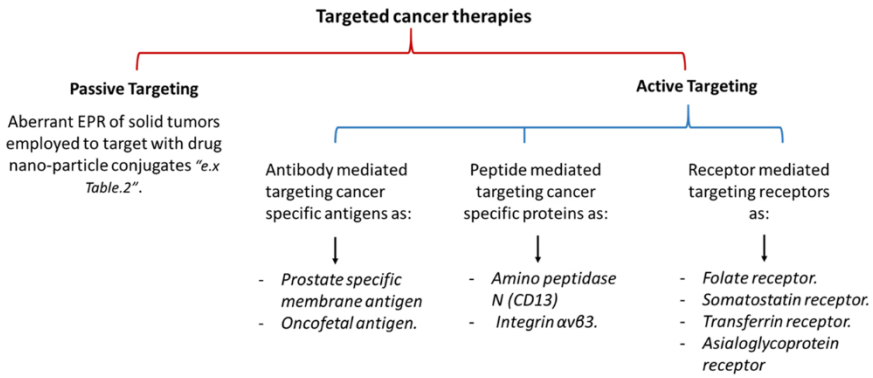

Fig. 8. summary of targeted cancer therapies. The figure shows different carriers and different strategies for targeted cancer therapy.

tumor cells displayed more than one highly expressed cancer marker, this encouraged the development of multi targeting complex composed of the drug in nanoparticles directed to more than one tumor marker [187]. Recently, the expanded knowledge and research in the field of the ligand targeted therapy enabled the development of FDA approved drugs for clinical use as CPX-351 (Vyxeos™) a recent FDA approved liposomal formulation of cytarabinee–daunorubicin combination [188]. Moreover, ligand targeted therapy has been described by several groups to be effectively applied in other pathologies as Sjögren's syndrome, rheumatoid arthritis and Alzheimer's disease [189–191]. More clinical trials are needed to study dual and multi targeting therapy that would contribute effectively for better prediction of clinical outcomes, and this will participate in successful therapeutic regimen development. Finally, modern technologies such as gene editing (CRISPR), mRNA-based vaccine, nanoparticles and cancer stem cells inhibition would play and contribute significantly to the advance of targeted cancer treatment and will contribute to overcome the pitfalls of traditional targeted therapies including and drug resistance and cancer recurrence.

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