IJBPAS, February, 2023, 12(2): 935-949

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

A REVIEW ON APPROACHES FOR TISSUE TARGETING DRUG DELIVERY

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Received 29th March 2022; Revised 28th April 2022; Accepted 17th July 2022; Available online 1st Feb. 2023

https://doi.org/10.31032/IJBPAS/2023/12.2.6892

ABSTRACT

Whenever some drugs which are not targeted are systemically administrated, they do not show desired efficacy and acceptable toxicity. Hence, the development of targeting approaches for site targeting drug delivery helps in reducing the toxicity and thereby improved therapeutic efficacy, unlike the non-targeted drugs. The literature studies that are done during the past years had understood the factors that are limiting the tissue targeting drug delivery and made some approaches that help in targeted drug delivery. Some of them include carbohydrates-based, protein-based, pathogen-based, mammalian cell membrane-based, small molecules-based, monoclonal antibody-based, Integrin-based, aptamer-based and we discussed how these approaches have a great potential in reducing/avoiding the level of toxicities and improving the quality of life and patient well-being.

Keywords: Tissue targeting drug delivery, targeting approaches, carbohydrates, monoclonal antibody, aptamer

INTRODUCTION

The development of targeted drug delivery is very much important now a day to achieve the targeted action of a particular drug and to avoid unwanted action of the drug in other parts of the tissues/organs that are not targeted. The difference between

conventional chemotherapy and targeted therapy in the treatment of the tumor tissue **[1] Figure 1**.

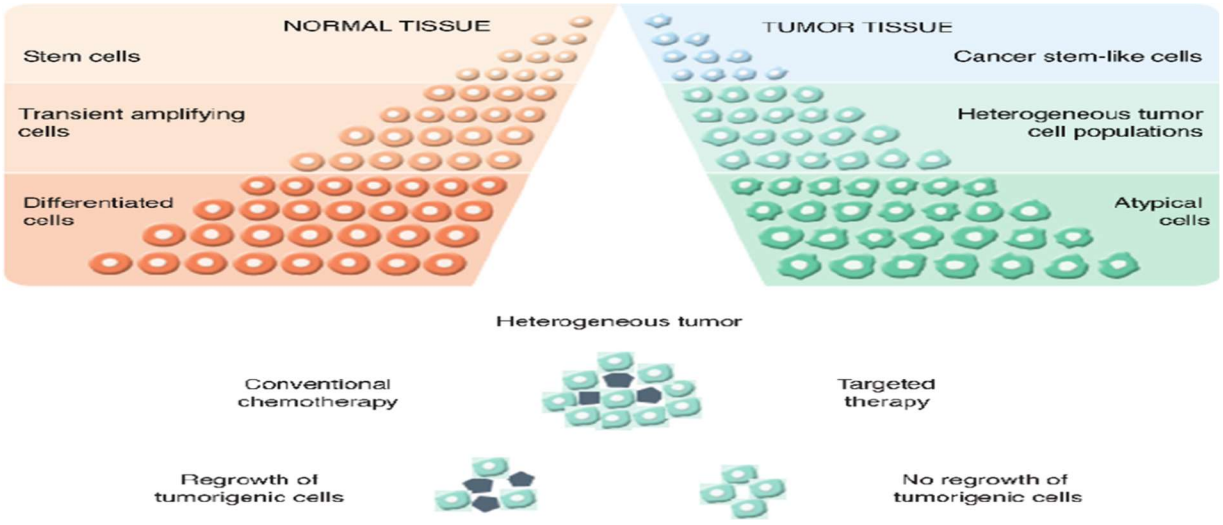

Figure 1: The difference between conventional chemotherapy and targeted therapy in the treatment of the tumor tissue [2]

Understanding the advantages, disadvantages, and applications of targeted drug delivery system is important and are mentioned below content.

TARGETED DRUG DELIVERY

Targeted drug delivery is a type of smart drug delivery system which is fantastic in delivering the drug to a patient. This conventional drug delivery system is done by the absorption of drug across a biological membrane, whereas the targeted release system is that drug is released in a dosage form **[3, 4]**.

CHARACTERISTICS OF TARGETED DRUG DELIVERY

- Should be biochemically inert.
- Should be non-immunogenic.
- In both in vivo and in vitro conditions, they should be physically and chemically stable.
- Must have a therapeutic amount of drug release.
- During the transit period, there should be minimal drug leakage.
- Carriers used are biodegradable and readily eliminated from the body **[5]**.

APPLICATIONS OF TARGETED DRUG DELIVERY SYSTEM

- It is used in 3D printing to analyze how to target cancerous tumors. By printing a plastic 3D shape of the tumor and filling it with the drug and show drug action at a targeting location of the drug.
- In proteins detection.

- In tissue engineering.
- In drug and therapy.
- By targeted drug delivery we can treat many diseases, such as cardiovascular diseases
- and diabetes. However, the most important application of targeted drug delivery is to treat cancerous tumors **[6]**.

ADVANTAGES

- A targeted drug delivery system decreases the side effects and toxicity.
- The dose of the drug decreases by targeting the organ.
- The degradation of the drug is avoided (first-pass metabolism).
- An increase in drug bioavailability and a decrease in fluctuation in concentration take place.
- In addition, it has a positive effect on the permeability of proteins and peptides.
- These all parameters in combination cause dosage frequency reduction and hence decrease the cost of expensive drugs.

DISADVANTAGES

- It is difficult to target the tumor cells with targeted drug delivery.
- Modern techniques and qualified persons are required.
- Sometimes it may cause toxicity and it is very difficult to maintain the stability of dosage forms **[7]**.

BIOLOGICAL BARRIERS FOR TISSUE SPECIFIC DRUG DELIVERY

Therapeutics that are administered intravascularly, experience biological barriers serially before reaching the target sites, and the complexity of these barriers depends on the properties of the therapeutics and their formulations. Here, we discuss key biological barriers that are faced by therapeutics. As the nature of the biological barriers is different for nanoparticle therapeutics, we also mentioned the barriers that are faced by nanoscale therapeutics **[8]**.

1. Intracellular barriers

Upon intravascular administration, therapeutics faced several intravascular barriers. Intravascular enzymes, such as proteases and nucleases, destroy the active ingredients, forming the first intravascular barrier. In addition, small molecule therapeutics and large molecule therapeutics of a certain size(<6nm) can be cleared via renal filtration**.** Nanoparticle therapeutics face additional intravascular barriers, including sequestration by the mononuclear phagocyte system(MPS), consisting of a

system of phagocytes, mainly resident macrophages lining the vascular wall in the liver (Kuffer cells) and spleen (Splenic macrophages) and monocytes in the bone marrow **[9]**. Upon entering the circulation, plasma proteins immediately get adsorbed onto the surface of the nanoparticles forming a protein corona (known as"Opsonization"). Opsonized nanoparticles are recognized by MPS through specific receptor binding and are eventually internalized by phagocytes. The endothelial barrier blocks therapeutics from extravasating into the target tissues.

2. Endothelial barriers

Endothelial cells line the vascular lumen and get attached to the underlying basement membrane and extracellular matrix tightly with the help of integrins. The integrity of the endothelial barrier varies depending on the specific tissues and their pathological conditions. The endothelial barrier between the blood and the brain (blood-brain barrier) is extremely restrictive because of the high density of endothelial cells and tight junctions present between them. In some disease conditions, like injury of tissue, cancer, and infection, the vascular endothelium undergoes dysfunction and fenestration, leading to the formation of a relatively leaky vessel, a phenomenon known as the EPR effect (enhanced permeation and retention). The EPR effect is particularly significant to cancer due to its aggressive angiogenic nature creating an opportunity to deliver therapeutics, especially nanoparticle therapeutics, to tumors. In case of inflammation, extravasation through leaky vasculature and inflammatory cell-mediated sequestration (ELVIS) can help in targeting drugs to inflammation sites**[10]**.

3. Extracellular barriers

On successful extravasation via the endothelial barrier, the therapeutics must penetrate via the extracellular matrix (ECM) to reach the cells of the targeted tissues. Generally, diffusion of small molecules is easy when compared to large molecules, even nanoparticles experience the problem of resistance in the ECM. In some disease conditions, the ECM environment can be changed, creating additional biological barriers. For example, tumors generally have very poor lymphatic drainage, a dense ECM, and widespread fibrosis. These parameters, together with the disrupted vasculature, lead o increased interstitial fluid pressure in the tumors, which includes the osmotic and hydrostatic pressures, therefore arrests the transport of small molecules through the vessels, and decreasing the extravasation of

large molecules and nanoparticles to the target cells.

4. Cellular barriers

Overreaching the tissue that is targeted, therapeutics with intracellular targets have to cross the plasma membrane to reach their targets that are present in the cytosol or nucleus of the cells. The plasma membrane is more permeable to hydrophobic small molecules. However, the transport of macromolecules and nanoparticles requires an active uptake mechanism, which in turn requires their efficient interactions with the plasma membrane and subsequent endocytosis processes, such as phagocytic, clathrin, and caveolae-mediated endocytosis. Macromolecules that are endocytosed and the nanoparticles are translocated to intracellular vesicles including endosomes, phagosomes, and lysosomes. These endosomal compartments have acidic pH and enzymes that favor the degradation of active therapeutics **[11]**. This creates an additional biological barrier. Therapeutics that are entrapped need to escape out from the endosomal compartments to reach their intracellular targets **Figure 2**.

Better knowledge and understanding of the above specified biological barriers have helped the development of so many effective targeting approaches for tissue targeting drug delivery.

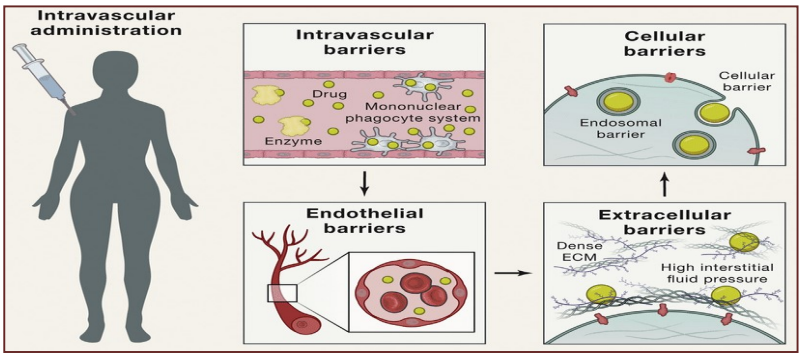

Figure.2: Various biological barriers that are faced by the tissue targeting drug delivery systems [1]

TARGETING APPROACHES FOR TISSUE TARGETING DRUG DELIVERY

Many targeting approaches are implemented to acquire the drug effect only in the targeted tissues/organs and not in non-targeted organs/tissues so that we can achieve high efficacy and reduced toxicity. Some of the targeting approaches are discussed in the following content.

1. CARBOHYDRATES BASED APPROACH

1.1. Simple sugars based

The targeting of simple carbohydrates receptors using naturally produced sugars is a very common method used for modulating

nanoparticles localization. One example is mannose, which is present on many types of cells. Mannose can also be used as a ligand to target cancer via tumor-associated macrophages, which allow the growth of tumors by releasing protein factors that stimulate tumor growth **Table 1**. A PEGylated nanoparticle platform has been reported that takes the advantage of this targeting mechanism **[12]**. Mannose-modified particles are coated in a pH-sensitive outer layer of PEG, which diffuses in low pH tumor microenvironments. This resulted in the exposure of a mannose functionalized layer that aids the efficient binding to tumor-associated macrophages and subsequent drug delivery.

1.2. Glycans and glycan-binding lectins based

Glycans represent more complex carbohydrates that are mostly expressed on either lipids or proteins, and these biomacromolecules have important implications in many natural binding interactions. They have been used to increase the biocompatibility and stability of nanoparticles in protein-rich solutions and to add lectin targeting abilities. In recent work, N-acetylglucosamine (GlcNAc) was used to modify gold nanorods. This modification reduced macrophage uptake in vitro and enabled the interaction of the nanoparticles with carbohydrates binding proteins [**13]**.

Table 1: Carbohydrates: carbohydrates coated drug delivery systems

Glyco-ligand	Target	Glycol-linker	Carrier	Drug	Ref
Gal	ASGP	Gal-C4	liposomes	probucol	[14]
Man-6P	M6P/IGF-II	Man-6P-HAS	HSA	Gliotoxin	[15]
Man	-	Oligomanose-DPPE	Liposomes	5-FU	[16]
Man	-	Oligomanose-DPPE	Liposomes	ovalbumin	[17]
sLeX	E-Selectin/tumor	sLeX-HAS-GL	Liposome	fluorescent	[18]
sLeX	E- Selectin/EC	sLeX-HAS-GL	Liposome	Dexamethasone	[19]

2. PROTEINS BASED APPROACH

2.1. Transferrin proteins based

Transferrins are glycoproteins that bind to iron ions in the serum and transport them to cells via transferrin receptors. These receptors can be highly overexpressed on some cancers and transferrin receptor targeting approaches represent one of the most studied methods for targeted delivery of therapeutics and imaging agents. Transferrin functionalization has been reported for many different nanoparticle platforms, including liposomes, polymeric nanoparticles (PNPs), gold nanoparticles **[20]**, and iron oxide nanoparticles. Interestingly, it was found in one study that functionalizing gold nanoparticles with transferrin has not significantly improved

their overall biodistribution, but it has strongly improved localization to certain cell types within different organs and within the tumors.

2.2. Lipoproteins based

The transportation of lipid involves High-density lipoproteins (HDL) and has involvements in many common diseases like heart disease and cancer. Due to its ability to target specific cell types, HDL particles have been used widely in drug delivery. Reconstructed HDL nanoparticles consisting of fluorescent calcium carbonate are used as a probe for the detection of lung cancer in vivo **[21] Table 2**.

3. PATHOGEN BASED APPROACH

3.1 Viruses based

Virus-like particles (VLPs) imitate naturally occurring viral capsids, and are studied for their capability to deliver different therapeutics **[23]**. These speak for a promising form of targeted delivery and therefore many viruses gained cellular entry through specific interactions with the cell surface receptors. For example, the human rhinovirus, which targets the ICAM-1 protein which is present on the surface of many immune cells Hepatitis B VLPs was loaded with iron oxide nanoparticles, and the resulting formulation could be efficiently taken up intracellularly for improved MRI contrast **Table 3**, **Figure 3**.

Table 2: Proteins Summary of albumin-based drug carriers in clinical studies

Mode of drug delivery	Drug name	Active pharmaceutical ingredient(API)	Indication	Clinical status	Ref
Albumin-drug conjugates	MTX-HSA	Methotrexate	Metastatic renal carcinoma	Phase II	[22]
Albumin-binding drugs /prodrugs	Victoza	GLP-1(7-37)	Type II diabetes	approved	
Bumin-based nanoparticles	Abraxane	Paclitaxel	Metastatic breast cancer; locally advanced/metastatic NSCLC; metastatic pancreatic adenocarcinoma	approved	

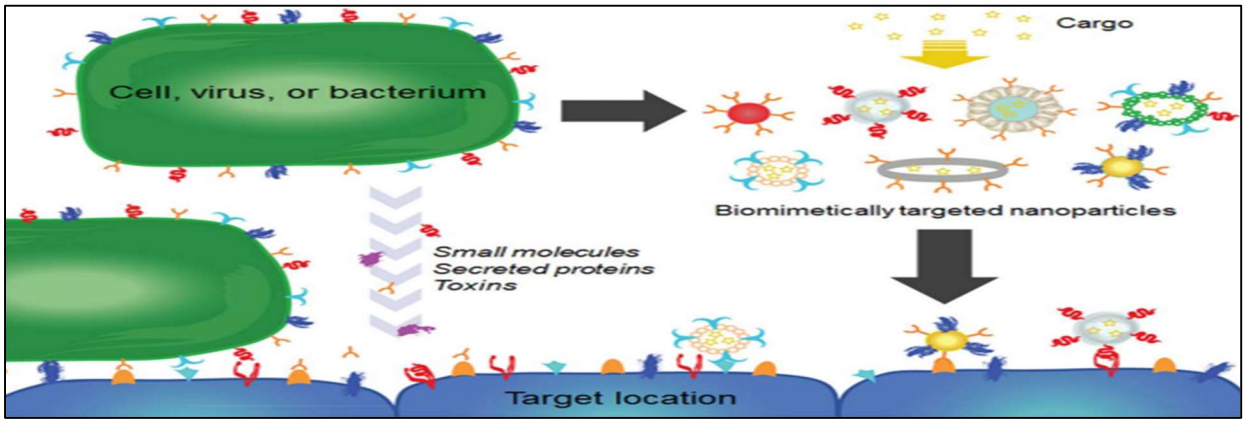

Figure 3: Cells, small molecules, proteins, and toxins - targeting affinities and many targeted nanoformulations are prepared by directly attaching them with the therapeutics [24]

Table 3: FDA approved or clinical trial stage VLP-based vaccines against infectious diseases

Trade name	Infectious agent	Target disease	Clinical trails status	Ref
Sci-B-vac™	Hepatitis B virus	Hepatitis B	Approved	[25]
Mosquirix ™	Plasmodium falciparum	Malaria	Approved	
Nanoflu ™	Influenza virus	Seasonal influenza	Phase 3	
Hecolin ™	Hepatitis E virus	Hepatitis E	Approved	

4. MAMMALIAN CELL MEMBRANES BASED APPROACH

4.1. STEM CELLS

Mesenchymal stem cells (MSCs) have unique tumor properties given that they are employed by tumors to improve their proliferation. These are mediated in part by direct cell-cell interactions suggesting the utility of stem cell-derived membrane for targeted delivery. "Nanoghosts" that are derived directly from the MSC membranes are recently reported as an important platform for prostate cancer targeted therapy **[26]**. The vesicles were loaded with soluble recombinant derivatives of TRAIL (sTRAIL) (TRAIL-TNF- related apoptosis inducing ligand) by a physical extrusion method and were shown to retain their tumor binding properties both in vitro and in vivo. Compared with free sTRAIL, the nano ghost formulation showed significantly improved control of tumor growth.

4.2. Platelets based

Platelets are very important in maintaining hemostasis and are the front line in wound healing, where they mediate the clotting cascade. Because of their complex nature, including the fact that their membrane displays numerous cell and extracellular matrix adhesion proteins, platelets are involved in many pathologies, including cancer, cardiovascular disease **[27]**, and infections. Cell membrane coated nanoparticles have recently been reported that imitate the natural function of the source cells **Table 4**.

Table 4: Cell membrane: Classification of cell membrane coated nanoparticles

Name	Coating membrane	Core materials used	Key features	Ref.
Cancer cell membrane coated NPs	Breast cancer cells, squamous carcinoma, melanoma	PCL NPs, PEG, -NaF4:Er3+, Yb3+, PLGA, iron oxide	Homotypic binding, anti-tumor response, immune tolerance and suppression	[28]
Mesenchymal stem cell membrane coated NPs	Mesenchymal stem cells	super magnetic iron oxide, Gelatin	Inhibition of inflammation, immunomodulatory activity, damaged tissue and tumor affinity, tumor homing ability, reduced RES capture	[29]
Platelets cell membrane coated nanoparticles	Platelets	PLGA, nano gel	Immuno-compatibility, high permeability and retention, injured vasculatures, tumor and pathogen affinity	[30]

5. INTEGRIN BASED APPROACH

In the tumor neovasculature, integrins are the small peptides that are expressed. They can be used in active targeting approaches that are focused on leading the chemotherapy agents to the cancer cells. For example, H2009.1 is a peptide with a high affinity for the cell receptor integrin v6 which has been successfully incorporated into DOX-loaded polyglutamic acid conjugates **[31]**. Flow cytometric analysis and fluorescent microscopy showed that the conjugates were selectively internalized into v6 positive cells. This cellular uptake was expected to be mediated by H2009.1 as there is no internalization of DOX-loaded polyglutamic acid was observed when it was conjugated with the control peptide. Integrin targeting has also been led to gene delivery to cancer **Table 5**.

Table 5: use of αvβ3 and/or αvβ5 integrin ligand in targeted gene delivery

Carrier system	Targeting motif	Gene	Cellular system	Results and Characteristics	Ref
PEG-PLys ployplex micelle	cRGDK	Luc-pDNA	HeLa cells and 293T cells	Enhanced transfection efficiency (TE) and perinuclear accumulation of pDNA within 3hrs of incubation	[32]
PEG-PEI polyplex micelles	Non-cyclic RGD-peptidomimetic	-	MeWo and A549 cells	Increased binding, uptake, and luciferase transgene expression in model cells	[33]
HPMA copolymers	cRGDK	Docetaxel	PC-3 and DU145 prostate cancer cell lines	Inhibition of PC3, DU145 cell growth, and also of HUVECs in vitro. In vivo tumor regression is also observed	[34]

6. APTAMER BASED APPROACH

Aptamers are nucleic acid ligands (DNA/RNA oligonucleotides) that can preferentially bind to target antigens. In cancer, they can be formulated directly for tumor treatment, but they can also be paired to drug delivery systems to increase the targeting of cancer cells **[35]**. For instance, doxetaxel loaded PEGylated poly (D, L-lactic-co-glycolic acid) (PLGA) nanoparticles were surface coated with A10 2-fluoropyrimidine RNA aptamers that identify the extracellular domain of the prostate-specific membrane antigen(PSMA), a surface antigen that was expressed on prostate cancer cells. It was explained that the PSMA proteins that are expressed on the surface of the cancer cells will subsequently be uptaken **Table 6**.

Table 6: APTAMER: AS1411-based targeting platforms for delivery of therapeutic agents

Targeting pathway	Drug	Target cell	In vitro/ In vivo	Ref
Aptamer-drug hybrid	Dox	Huh7	Y/Y	[36]
PEG-PLGA	Gemcitabine	A549	Y/N	[37]
DNA dendrimer nanostructure	MCF-7,C26	Epi	Y/Y	[38]

7. SMALL MOLECULES BASED APPROACH

Small molecules with more various structures and properties are less costly to produce and have great potential as a class of targeting moieties. One of the most studied small molecules as a targeting moiety for the delivery of agents is folic acid (folate). Folate receptors are frequently overexpressed by cancer cells as a consequence of increased folate requirements for DNA synthesis. The interaction of a folate moiety with the folate receptor on tumor cells leads to an endocytic transport that results in cytosolic accumulation **[39]**. Polymeric nanoparticles have also been surface coated with folate and its derivatives to induce selective drug targeting. Anticancer prodrugs have also been coated on the drug carrier's surface that is functionalized with folate to improve their cellular uptake and cytotoxicity **Table 7**.

Table 7: Small molecules: Representative Clinical Trials for Small Molecule-Based Targeting Strategies

Target agent	Targeted mode used	Clinical indication	Identifier	Clinical trails status	Ref
Folicacid/folate	vintafolide (EC145)+ etrafolide (EC20)	Ovarian cancer, endometrial cancer	NCT00507741	Phase II (completed)	[1]
	EC0225 +EC20	Refractory or metastatic tumors	NCT00441870	Phase I (completed)	
	vintafolide (EC145)+ etrafolide (EC20)	Triple-negative breast cancer	NCT01953536	Phase II (withdrawn)	

8. MONOCLONAL ANTIBODIES BASED APPROACH

FDA-approved monoclonal antibodies (MAbs) can be employed against several surface antigens or receptors of tumor cells. Immunoliposomes (liposomes conjugated with MAb) can be prepared by either attachment of the MAb directly to the liposome phospholipids head group or PEG endings. The human epidermal growth factor receptor-2 (HER-2) is the one particular target of immunoliposomes. Several investigations have been conducted and shown that DOX-loaded anti-HER-2 immunoliposomes are capable to display improved therapeutic efficacy towards different breast cancer xenograft models when compared to naked PEGylated liposomes **[40] Table 8**.

Table 8: Mab: Monoclonal antibodies specific to brain endothelial cell receptors and their reactivity

Targeting mAb	Target receptor	Reactivity	Ref
Humanized anti-IR	Insulin receptor	Human	[41]
Anti-E-selectin	E-selectin	Human	[42]
R17217	TfR	Mouse, human	[43]

CONCLUSION:

In conventional targeting approaches, which often depend on methods involving lengthy discovery and validation, the use of naturally occurring binding mechanisms has the potential to speed up workflows for new targeting ligand identification. Interactions for binding among cells, small molecules, biomolecules, and surfaces are a fundamental part of biological systems, and the character of these interactions can vary greatly depending on the biological function. As mentioned in this review, naturally targeting approaches can be implemented using anything i.e from small molecule vitamins to entire cell membranes.

In the future, it can be visualized that multiligand approaches for targeted nanoparticle delivery will be increasingly investigated. Generally, most targeted therapies have been implemented in cancer management and their use in other disorders has not been implemented as broadly as in cancer. For this reason, the field that is moving towards cell-based approaches or other conditions like autoimmune diseases is being increasingly investigated. Tissue targeting drug delivery has a great potential in reducing/avoiding the level of toxicities and hence improves the quality of life and patient well-being.

ACKNOWLEDGEMENTS: We express our sincere thanks to Dr.Y.Srinivasa Rao, Principal Dr.P.V.Kamala Kumari, Professor and Dr.L.Rathaiah, Chairman Vignan Group of institutions for providing facilities and encouragement to carry out the above review.

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