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LIGAND MEDIATED TARGETED DRUG DELIVERY SYSTEM

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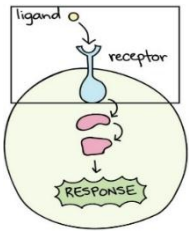
ABSTRACT
This paper is an overview of advance and prospects in application of nanotechnology for cancer treatment. Cancer is the foremost causes of death worldwide. Passing away from cancer are continuously rising worldwide with a projection of about 12million are passing away from cancer. So, we are using the ligand targeted therapy (LTT). The Most cancer medicines are designed to impede with one or more events in the cell proliferation. As healthy cells may also require to proliferate and circumvent apoptosis, anticancer agents can be toxic to such cells. To diminish these toxicities, strategies have been developed wherein the therapeutic agent is targeted to tumour cells through conjugation to a tumour-cell-specific small-molecule ligand, thereby reducing delivery to normal cells and the associated collateral toxicity. This Review describes the major principles in the design of ligand-targeted drugs and provides an overview of ligand–drug conjugates and ligand–imaging-agent conjugates that are currently in development It is a powerful pharmaceutical strategy to achieve selective drug delivery to pathological cells, for both therapeutic and diagnostic purposes, this active drug targeted approach is based on the discovery that there are receptor overexpressed on pathological cells, compared to their expression in normal tissues. Recent studies high lights the ligand density plays an important role in targeting efficacy. Furthermore, LTT applications in diseases form cancer and those exploiting receptor overexpressed at cytoplasmic level are growing.

KEYWORDS: Cancer, Toxicity, Tumour, Ligand, Liposomes, Receptor mediated targeting.

INTRODUCTION
The Cancer is foremost causes of passing out worldwide especially in those countries having low and middle financial condition. An important approach for selective drug delivery to pathological cells is the use of targeting strategies involving the conjugation of targeting molecules to the drug or to drug loaded nanocarriers [e.g. Liposomes, Nanoparticles etc.] Active targeting is also called ligand based targeting. Active targeting involves attaching to the drug system something like an antibody or carrier protein or ligand.

LIGAND
What is ligand?
A ligand is some molecule which we attach to the drug delivery system, which acts as homing device and takes the delivery system to the target. LIGAND binds to receptors. Let us study a few of these ligands which are our homing devices used in active targeting.

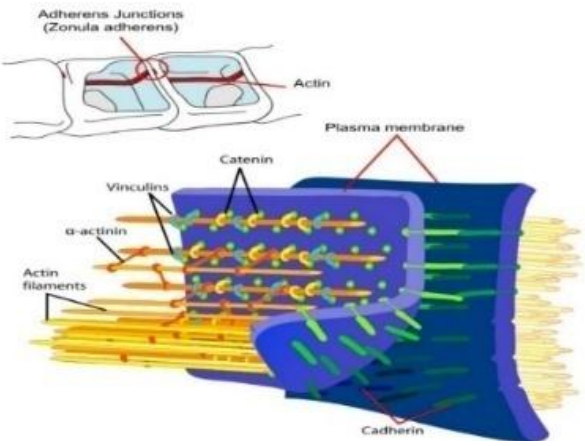


"Fig. 1"Ligand binds to the receptor.

(A) Antigens
(B) Catherine

(A) Antigens: Tumours have the property of expressing certain specific type of antigens. One strategy in treatment is to send delivery system to which antibodies to these antigens are attached as ligand so that by the antigen-antibody reaction the delivery system will be localized in the Tumour and drug will be released there. The carcinoembryonic antigen, is expressed in breast Tumour, lung tumours and gastrointestinal tumours.

(B) Cadherin: Cadherin are glycoprotein, they are used to facilitate calcium ion dependent cell-cell.



"Fig.2" Principal interactions of structural proteins at cadherin-based adherence junction. Actin filaments are linked to α-actinin and to membrane through vinculin. The head domain of vinculin associates to E-cadherin via α-, β-, and γ-catenin. The tail domain of vinculin binds to membrane lipids and to actin filaments.

Adhesive interactions. In addition to these selections, integrins and vitamins may be used as ligands. Transferrin, which is used as a carrier molecule in transport may be used as ligand**.**

Antibodies, hormones and low density lipoproteins were also used as ligand for active targeting. So, useful type of targeting.

LIGAND	TARGET
Folate	Folate receptor
Transferrin	Transferrin receptor
Galactosamine	Galactosamine receptor on hepatocytes

Ligands Are carrier surface groups which can selectively direct the carrier to the perspective site housing the appropriate receptor units to serve as 'homing device' to the carrier/drug.

Most of the carrier system are colloidal in nature and can be specifically fictionalized using various biologically relevant molecular ligand including antibodies, polypeptides, polysaccharides, viral protein and cryogenic residue.

The ligand confer recognition and specificity upon drug carrier and endow them with an ability to approach the respective target selectively and deliver the drug.

Here the carrier for the drug is made specific for the certain cell or group of cells by incorporating ligand. Such as antibody, polypeptides, oligosaccharides etc., on the surface of the carrier**.**

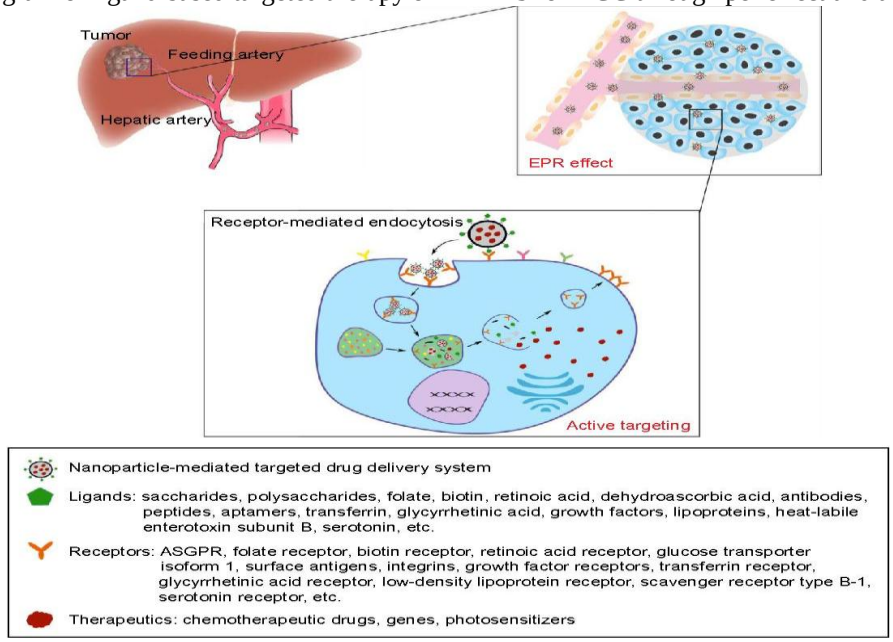
(A) FEATURES OF RECEPTORS, LIGAND AND LIGAND DRUG CONJUGATED FOR LIGAND TARGETED THERAPY

1. A receptor should be present in high density on the pathological cells, but be almost absent or in accessible in normal ones.
2. The specificity for the ligand and its ability to be internalized and recycled back to the call surface for another round of ligand binding and endocytosis process.
3. An ideal ligand for ligand targeting therapy should possess high binding specificity to the cell surface receptor.
4. It should have significant impact on the drug release kinetics.

Examples of ligand targeted therapy

1. Ligand that bind directly to a receptor over expressed on a pathological cell surface.
2. Direct conjugation of targeting molecules to the drug results in targeting molecule to drug results in targeting therapy,while conjugation of targeting molecules to nanocarriers is associated with a targeted delivery allowing the administration of large quantities of unmodified drug.
3. In both cases ligand targeted therapy (LTT) occurs.
4. Apoprotein coat serves as ligand for LDL receptor.

The schematic diagram of ligand based targeted therapy of NTDDS for HCC through per effect and active targeting.



"Fig. 3" Receptor mediated endocytosis.

ABBREVATIONS

NTDDS- Nanoparticles-mediated targeted drug delivery system.
HCC- Hepatocellular carcinoma.
ePR-enhanced permeability and retention
ASGPR- asialoglycoprotein receptor.

Selected examples of nanocarriers employed LTT. Examples taken from the literature up 2008.

Nanocarrier	Targetingmolecules	Results
PLGAnanoparticles	Transferrin	conjugated to transferrin (TF) ligandin breast cancer cell line were studied. NPs were formulated utilizing poly (lactic-co-glycoside) (PLGA), with encapsulated Tx and conjugated to Tf ligand via an epoxy linker. Tf conjugated NPs demonstrated greater and sustained antiproliferative activity of the medication in dose and time dependent studies compared to that with drug in solution or unconjugated.
PLA-PEGnanoparticlesand abiding-biotin technology	Transferrin	*In vitro* :paclitaxel was incorporated both in biotinylated (BP) and biotinylated (LP) PEG -PLA nanoparticles GP and LP Nanoparticles achieving over 90% paclitaxel incorporation were obtained . No nanoparticles were targeted to glioma Cells by three step avidin-biotechnology using transferrin as targeting ligand.
PG-TUMOR necrosis factor alpha (PG -TNF-alpha) conjugates	Transferrin	*In vivo:* PEGylated recombinant human Tumournecrosis factor alpha was modified with Tf to form Tf-PEG-TNF -alpha conjugates j PEGylated ligation reactions 4PEG-TNf-alphaconjugates with different PEG chains was synthesized and denoted as PT1,PT2,PT3,PT4 respectively. The results demonstrated that TPT4 bounce specifically to the TfR on the Tumour cell surface and affinity of the conjugated Tf was similar to that of native Tf. In contrast, PG-TNF-alpha demonstrate no specificity.
DC-Chol/egg PC/PEG -DSPE liposomes	Transferrin	*Invitro*: liposomes composed of DC-Chol/Egg PC / PEG-DSPE were loadedwith an antisense oligo deoxy robot nucleotide (G3139). To prepare targeted Liposomes, transferrin was first coupled to PEG-DSPE and then incorporated in to the bilayer by post –insertion.
Dendrimers	Transferrin	In vitro and In vivo: A brain – targeting gene vector based on the polyamido amine (PAMAM)Dendrimer was studied.

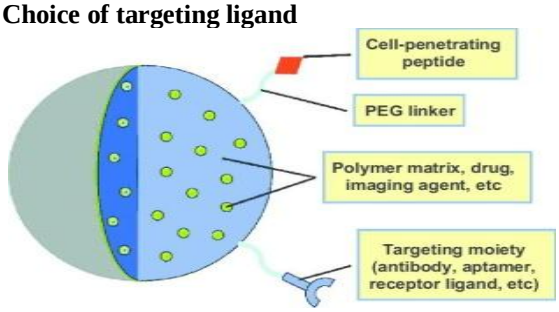
(B) PEPTIDESANDPROTEINRECEPTOROVERE XPRESSEDATCYTOPLASMIC LEVEL

Besides the peptide receptors over expressed on a pathologicalcells as those above consider, there is a experimental evidence suggesting that also peptide receptors located at cytoplasmic level can also play an important role in targeted delivery of both chemotherapeutic and imaging agents. Actually, pharmaceutical nanotechnology as applied at the sub cellular level is new frontier in LTT. More effective employment of TSPO ligand as therapeutic vectors or as targeting moieties for drug delivery system would have the potential to achieve an even greater therapeutic effect.

Selected examples of peptide -receptor targeted nanocarriers or conjugated.

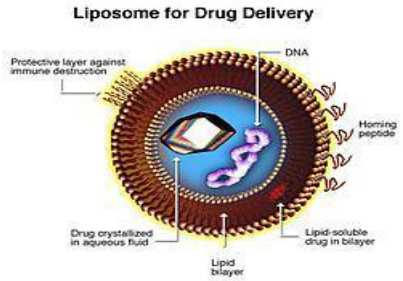
Nanocarriers	Peptides	Results
Protamine based nanoparticles	VIP	In vitro and ex vivo: The receptor for vasoactive intestinal peptide (VIP), are overexpressed by various Tumour cells. The cell binding triggered the conjugate internalization of VIP-conjugated molecules In vitro and ex vivo by human tumours (Partner at al., 2010).
Gonadotropin-releasing hormone (GnRH)and somatostatin conjugate	GnRH and Somatostatin	In vitro: In contrast to other regulatory peptides that stimulate the Tumour growth, GnRH and somatostatin derivatives have inhibitory effect; Therefore, they were used primarily for thepreparation of various conjugates to be used in treated chemotherapy, targeted radiotherapy, Photodynamic therapy, boron neutron capture therapy and cancer diagnosis. Some of these conjugates have already realised clinical applications, whereas others are currently in preclinical and clinical

1. Choice of targeting ligand

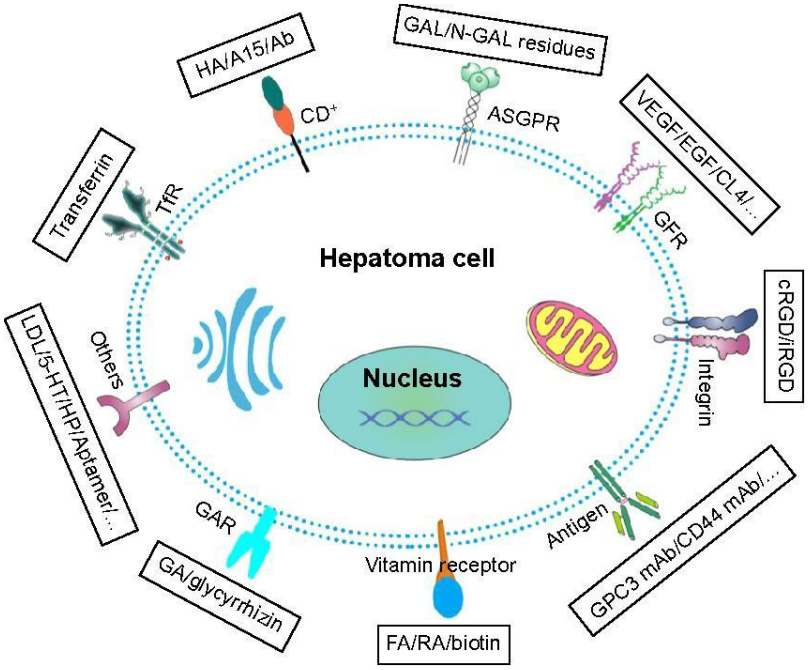


Liposomal anticancer drugs may be targeted by means of small ligands, peptides, or antibodies and fragments ofantibodies. IL/SIL can be targeted with whole monoclonal antibodies or fragments of antibodies. Antibodies and antibody fragments have been widely used for targeting liposomal drugs because they have the advantage of being highly specific for their target antigens, relative to other classes of targeting agents. In addition, synergistic activity may be observed when signalling antibodies are combined with combinations of anticancer drugs. However, the production of antibodies and fragments, which require expression and purification from biological systems, is much more cost-intensive than the production of small ligands and peptides, which, although they have lower target specificity, can be chemically synthesize.

2. Ligand-targeted liposomes



Liposomes are combination structures made of phospholipids and may contain small amounts of other molecules. Though liposomes can vary in size from low micrometre range to tens of micrometres, unilamellar liposomes, as pictured here, are typically in the lower size range with various targeting ligands attached to their surface permit for their surface adjunct and gathering in pathological areas for treatment of disease.Although Stealth liposomes and ligand-targeted Stealth liposomes both reach tumour tissues by the same mechanism, that is, passive distribution to the tumour cells via the bloodstream, the similarities end there. Only ligand-targeted nanoparticles bind selectively to target cells, such as tumour cells. When the ligand is chosen so that it binds to an antigen or receptor that triggers receptor-mediated endocytosis, then the whole particle, including its cargo of therapeutic molecules, is internalized into the target cell. Ligand-targeted liposomes may also have advantages over non-targeted liposomes in other situations, for example against micro-metastases that have yet to develop a vasculature, or when directed against tumour vasculature endothelial cells or other targets readily accessed from the vasculature. In addition to the specific delivery of anticancer drugs to antigen-expressing cells, synergistic effects may be achieved when anticancer drugs are delivered by means of IL or SIL targeted with antibodies that are capable of initiating antiproliferative or antiangiogenic signals. Therefore, some clear advantages exist for the targeted delivery of liposomal anticancer drugs over non-targeted liposomes.



"Fig.4"Receptor over expressed onHepatomacell.

The receptor over expressed on hepatoma cell and their ligands for targeted therapy of HCC.

ABBREVATIONS

HCC- Hepatocellular carcinoma
TFR- Transferrin receptor
FA- Folic acid
RA- Retinoic acid
GA- glycyrrhetinic acid
VeGF- Vascular endothelial growth factor
EGF- Epidermal growth factor
LDL- Low density lipoprotein

FURTHER DIRECTIONS

1. Combination of immune liposomal drugs

Examination of different combinations of immune liposomal drugs, containing either different drugs and/or different targeting agents, could result in enhanced efficacy. So far, only a few studies have examined the therapeutic effects of combinations of SIL drugs and/or targeting agents. In a model of neuroblastoma, Pastorino et al. treated mice with liposomal DXR targeted by means of mixtures of an anti-GD2 mAb or (tumour cell-targeted), and an NGR-peptide (tumour vasculaturetargeted) and also were able to demonstrate additive activity over either ligand used alone. Furthermore, Pastorino demonstrated that doxorubicin and an anti- c-myc antisense oligodeoxynucleotides delivered via anti- GD2-targeted liposomes were more effective than either agent alone. These studies showed that combining either drugs or antigens can result in increased therapeutic effects over monotherapies of immuno- liposomal drugs. Co-encapsulation of two different anticancer drugs in the same liposome have recently been described, making it possible to investigate the therapeutic effects of bispecific immunoliposomes co-encapsulating a combination of drugs.

2. New antibody constructs bispecific antibodies

New antibody constructs, such as bispecific antibodies, may be useful for targeting liposomal drugs. Bispecific (bs) antibodies can be used as a pretargeting agent for liposomes. In one example, a bsmAb with an anti-tumour domain and an anti-biotin domain was injected and allowed to localize in the tumour before initiating treatment with biotinylated liposomal drug Alternatively, immunoliposomes can be conjugated with bsmAb targeted against a tumour antigen and an antigen on effector cells, for example CD16 on NK cells.

ADVANTAGES

In ligand targeted therapy LTT two important advantages can be achieved:

A. It is possible to limit the distribution of drug selectively to pathological cells, minimizing the damage to healthy cells.

B. Ligand targeted therapy LTT can also be used for intracellular delivery of drug, such as protein based pharmaceutical and other macromolecular drugs, that cannot penetrate cell membrane efficiently. It is impossible to exploit so called "Receptor mediated endocytosis"(RME).

APPLICATIONS

1. Targeted drug delivery can be used to treat many diseases, such as the cardiovascular diseases and diabetes.
2. The most important application of targeted drug delivery is to treat cancerous tumours.
3. The passive method of targeting tumours takes advantages of the enhanced permeability and retention effect.
4. When the blood vessels form so rapidly, large fenestrae result that are 100 to 600 barometers is size which allows enhanced nanoparticles entry.
5. The key to solving the problem lies in the effective use of pharmaceutical drugs that can be targeted directly to the diseases tissue.
6. This technique can help develop many more regenerative technique to cure various disease represents a paradigm shift away from conventional approaches that aim to manage heart disease.
7. Stem cell therapy can be used to help regenerate myocardial tissue and return the contractile function of the heart by creating or supporting a microenvironment before the MI.
8. Liposomes can be used as drug delivery for the treatment of tuberculosis. The traditional treatment for Tuberculosis is skin to chemotherapy which is not overly potent, which may be due to the failure of chemotherapy to make a high enough concentration at the infection site.
9. The liposome delivery system allows for better macrophage penetration and better build a concentration at the infection site.
10. The delivery of the drug works intravenously and by inhalation. Oral intake is not counsel because the liposomes break down in the gastrointestinal system.
11. 3D Printing is also used by doctor to investigate how to target cancerous tumours in a more efficient way.
12. By printing a plastic 2D shape of the Tumour and filling it with the drug used in the treatment, the flow of the liquid can be observed allowing the modification of the doses and targeting location of the drug.

LIMITATIONS OF LTT

1. Targeted drug delivery technologies based on LTT has become very significant in the field of cancer therapy and immunoconjugate targeted delivery system.
2. Most potent drug can be targeted to a pathological cell if they can be linked reversibly to a targeting ligand with specificity for that cell type.
3. LTT may have particular potential for overcoming drug resistance because these ligands are usually internalized (RMR) Receptor mediated endocytosis.
4. It has been suggested that these targeted nanocarriers may be able to p-glycoprotein mediated resistance.
5. It may avoid recognition by the reflux pump.
6. However, in the development of LTT there are still many limitations i.e,

Oral bioavailability
Instability in circulation
In adequate tissue distribution
Toxicity as well as the difficulties of preparation in large scale and formulation.

Among these limitations, it should be also remembered that, because must endocytic pathways transport relatively few molecules into a cell, the ligand targeted drug must be effective at low concentrations.

CONCLUSION

With the current advances in antibody technology and the clinical acceptance of antibodies as a treatment modality, it is time for liposomes to progress from a passive targeting platform into an active, antibody-targeted drug delivery platform. Targeted liposomes are complex systems and various factors, including the size of the liposomes, antibody coupling methods as well as the targeting agent used. Single chain provides some clear advantages over, such as reduced molecular mass and improved pharmacokinetics of targeted liposomes.

LTT is a powerful means for delivering molecules into targeted cells for therapeutic and diagnostic purposes with limited side effects and toxicity. As mentioned above, several groups have reported improved delivery of targeted nanocarriers, as compared to nontargeted ones, to pathological cells. Over the past few years there has been a sharp growth of interest for LTT and the progress made, widely expanded this research area. Thus, recent studies have clearly pointed out that besides high ligand binding specificity, the ligand density on the nanocarrier (i.e. “the ligand content”) plays an important role in targeting efficacy in order to get an efficient ligand-receptor interaction.

Besides the expanded knowledge in this area, also two most relevant developments have been registered in the last two years. The first refers to the fact that some ligand-targeted therapeutic agents entered clinical trials for various cancers, and it sure will be useful for evaluating the clinical potential of LTT.

ACKNOLEDGEMENT

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REFERENCES

1. Cheng WW. Targeted delivery of immune liposomal doxorubicin to Cheng & Allen Expert Opin. Drug Deliv., 2010; 7(4).
2. Allen, T. M. *Ligand-targeted therapeutics in anticancer therapy*. Nature Rev. Cancer, 2002; 2: 750–763.
3. Van der Meel, R., Vehmeijer, L. J., Kok, R. J., Storm, G. & van Gaal, E. V. *Ligand-targeted particulate Nano medicines undergoing clinical evaluation: current status*. Adv. Drug Deliv. Rev, 2013; 65: 1284–1298.
4. https://doi.org/10.1021/acs.chemrev.7b00013
5. https://www.ncbi.nlm.nih.gov/m/pubmed/21942529/

6. https://www.ncbi.nlm.nih.gov/pubmed/19817715
7. Vlerken, L. E. V.; Vyas, T. K.; Amiji, M. M. Poly(Ethylene Glycol)-Modified Nanocarriers for Tumor-Targeted and Intracellular Delivery. Pharm. Res., 2007; 24: 1405–1414.
8. Bertrand N, Leroux JC.; Leroux. "The journey of a drug carrier in the body: an anatomophysiological perspective". Journal of controlled Release. 2011; 161(2): 152-63. doi:10.1016/j.jconrel.2011.09.098. PMID 22001607.
9. "Definition of targeted therapy - NCI Dictionary of Cancer Terms".
10. Targeted Cancer Therapies". National Cancer Institute.