Targeted Drug Delivery:

INTRODUCTION:

The biological effects of a drug in a patient depend upon the pharmacological properties of the drug. These effects arise due to the interaction between the drug and receptors at the site of action of the drug. However, the efficacy of this drug-target interaction stands undermined unless the drug is delivered to its site of action at such a concentration and rate that causes the minimum side effects and maximum therapeutic effects, Targeted drug delivery aims to achieve the same.

Targeted drug delivery, also known as smart drug delivery, is a method of treatment that involves the increase in medicament in one or few body parts in comparison to others. Therefore, it delivers the medication only to areas of interest within the body. This offers an improved efficacy of treatment and also reduces side effects. It differs from the conventional drug delivery system in that, it gets release in a dosage form while the former functions by the absorption of drug across biological membrane.

Greogoriadis, in 1981, described the use of novel drug delivery for drug targeting as „old drug in new clothes" Conventional dosage forms such as injections, oral formulations comprising of solutions and suspensions, tablets, capsules, and topical creams & ointments, possess certain innate disadvantages. Parenteral delivery of drugs is highly invasive with ephemeral effects. Oral administration of drug, in spite of being immensely popular and appropriate, cannot be used for certain drugs, such as protein or peptide drugs, owing to their poor absorption by the oral route. These may be degraded in the gastrointestinal tract. Topical creams and ointments have a drawback of being limited to local effects, rather than systemic ones. Currently drug delivery technology has become refined and it takes into consideration, several factors such as bioavailability, drug absorption processes, pharmacokinetic processes, timing for optimal drug delivery, etc.

There are four principle requirements for a successful targeted drug delivery system:

Retain evade target release

i.e., there should be proper loading of the drug into an appropriate drug delivery vehicle, it must possess an ability to escape the body‟s secretions that may degrade it, leading to a long residence time in circulation and thereby reaching the site of interest and, should release the drug at the specific site within the time that calls for effective drug functioning. Different sites of interest within the body necessitate the use of different drug delivery systems, depending upon the route to be followed.

PROPERTIES OF TARGETED DRUG DELIVERY

- It should be nontoxic, biodegradable, biocompatible and physicochemical stable invivo and invitro
- Confine drug delivery to target cells or tissue or organ or should have uniform capillary distribution.
- Predictable and Controllable and rate of drug release.
- Drug release should not influence the drug delivery.
- Therapeutic amount of drug release.
- Minimal drug leakage during transit
- Carrier used should be biodegradable or readily eliminated from the body without any problem and no carrier should induce modulation of diseased state.

COMPONENTS OF TARGETED DRUG DELIVERY

Target:

Target means specific organ or a cell or group of cells, which in chronic or acute condition need treatment.

Carrier or marker:

Carrier is one of the special molecule or system essentially required for effective transportation of loaded drug up to the pre selected sites. They are engineered vectors, which retain drug inside or onto them either via encapsulation and/ or via spacer moiety and transport or deliver it into vicinity of target cell.

Drug Targeting strategies:

Passive targeting

This is based on the accumulation of drug at areas around the site of interest, such as in case of tumor tissues. This is called Enhanced Permeability Retention (EPR) effect. Such a types of targeting occurs with almost all types of drug delivery carriers. Passive targeting is actually a misnomer because it cannot really be described as a form of selective targeting. Although the EPR effect applies for nanoparticle administered, the majority (>95%) of these nanoparticles tend to accumulate in organs other than those of interest such as liver, lungs and spleen. Thus, it is the distribution of drug by blood circulation. Examples include the use of antimalarial drugs being targeted for the treatment of microbial infections such as leishmaniasis, candidiasis and brucellosis.

Active targeting

Through the use of ligand-receptor interactions, active targeting describes the drug targeting interactions. However, interactions between a ligand and a receptor are possible only when the two are in close propinquity, (i.e. less than about 0.5mm). The currently available drug delivery systems are able to reach the target by the virtue of blood circulation and extravasation. Therefore, we can conclude that active receptor targeting actually means ligand-receptor interaction but that takes place only after blood circulation and extravasation. Active targeting can further be divided into three different targeting levels.

First order targeting

This is the distribution of drug to capillary beds of target sites- organ or tissue, for example, in case of lymphatic tissue, peritoneal cavity, pleural cavity, cerebral ventricles, eyes, joints, etc.

Second order targeting

This is the targeting of drugs to specific sites such as the tumor cells, for example, to kupffer cells in liver.

Third order targeting

It is the type of drug targeting wherein the drug is intracellularly localized at the target site via endocytosis or through receptor-based ligand mediated entry.

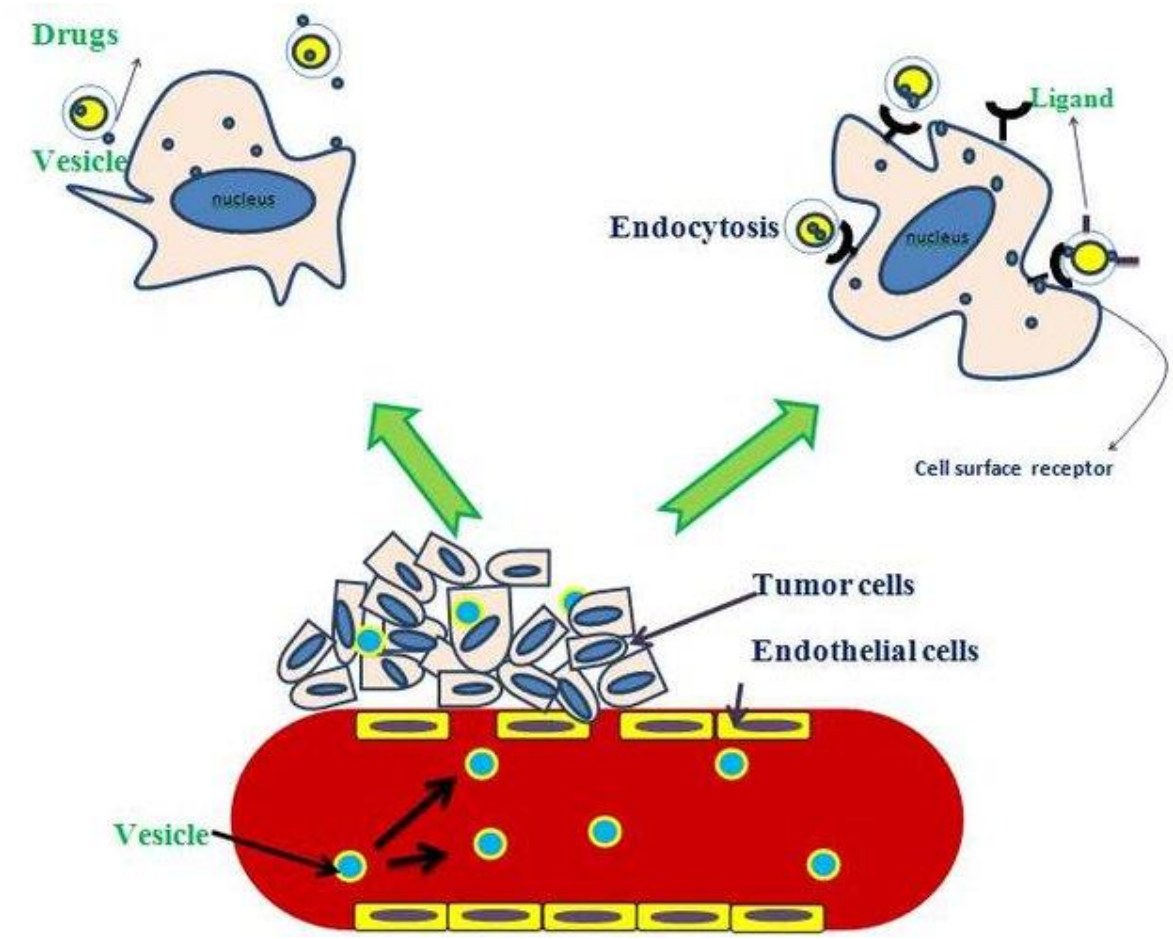

Fig: passive VS Active targeting

Dual Targeting:

In this targeting approach carrier molecule itself have their own therapeutic activity and thus increase the therapeutic effect of drug. For example, a carrier molecule having its own antiviral activity can be loaded with antiviral drug and the net synergistic effect of drug conjugate was observed.

Double Targeting:

When temporal and spatial methodologies are combined to target a carrier system, then targeting may be called double targeting. Spatial placement relates to targeting drugs to specific organs tissues, cells or even subs cellular compartment. whereas temporal delivery refers to controlling the rate of drug delivery to target site.

Nanoparticulate drug delivery systems:

1. Nanoparticles:

The National Nanotechnology Initiative (NNI) defines nanoparticles as structures with all three dimensions within the nanoscale (1-100 nm). Nanoparticles can modify or imitate the process occurring in living organisms. Nanoparticle-based targeted drug delivery systems have only recently been reviewed. These can be constructed for drug delivery across a number of biological barriers. It has been investigated that these can even cross the blood brain barrier (BBB).

2. Liposomes

Liposomes are the first to be explored as drug delivery vehicles. These are vesicles composed of an aqueous core bounded by a hydrophobic lipid bilayer. Solutes in the core, such as drugs, cannot overcome the hydrophobic barrier. However, the bilayer allows for the absorption of hydrophobic molecules and therefore, liposomes are known to be ampiphilic carriers. Liposomes differ in composition, size, number of layers, etc. These can either have a single bilayer, known as "unilamellar" or multiple bilayers, termed as "multilamellar". Unilamellar vesicles are further grouped into small unilamellar vesicles (SUVs) and large unilamellar vesicles (LUVs) according to their size (Vemuri and Rhodes, 1995). Drugs held and delivered by liposomes have significantly improved pharmacokinetic properties such as the therapeutic index. Also, these have a quick metabolism action, lower toxicity apart from in vitro and in vivo anti-cancerous activity. The encapsulation of drugs by liposomes leads

to the prevention of their untimely degradation.

3. **Dendrimers**

Dendrimers are synthetic, unimolecular, branched nanostructures (approx. 20 nm in size) comprising a core or focal point, multiple branched layers of repeated units and high density function terminal group. The functional group regulates the biocompatibility and physical, chemical properties of dendrimers. The molecular structure of dendrimers makes it possible for them to carry different drugs . The drugs may either be encapsulated in the core via hydrogen bonding, hydrophobic interaction or chemical bonding or these can be adsorbed via covalent bonding on the terminal groups

4. **Quantum dots**

are nanocrystalline semiconductors that range in size from 2 to 10 nm in diameter. Their size increases approximately two-fold after encapsulation by a polymer. These nanocrystals possess distinctive optical properties and are therefore, widely used in the fields of imaging and detection. Hydrophobic drug molecules can be implanted between the core and the layer of polymer cladding.Quantum dots are now found to be efficient enough to carry out targeted drug delivery and imaging of this process concurrently. This is particularly useful in the case of cancer diagnosis and treatment.

5. **Niosomes**

are self assembled microscopic vesicles composed of non-ionic surfactants and cholesterol. The non-ionic surfactants belong to the class of alkyl or dialkyl polyglycerol ether and they align themselves in a way so as to form a bilayer. Therefore, their structure is analogous to liposomes which possess a bilayer composed of phospholipids.

6. **Therapeutic monoclonal antibodies**

Monoclonal antibodies (mAbs) are molecules produced in the laboratory such that they adhere to distinct defects in cancerous cells. They imitate the natural antibodies in the body. Monoclonal antibodies are engineered by either “hybridoma technology” or “antibody libraries”. Monoclonal antibodies that possess a high binding affinity as well as specificity towards any target antigen are generally produced using antibody libraries.

7. **Nanocapsules**

Nanocapsules are miniscule vesicles comprising a solid/ liquid core with a cavity in which the drug

is inserted. The cavity is enclosed by polymeric membrane. Small interfering RNA or silencing RNA (siRNA), a type of synthetic double-stranded RNA, enveloped in nanocapsule, can be used for targeting estrogen receptor alpha (ER- α), also called NR3A1. Studies have shown that remarkable reduction in tumor growth (an expression of ER- α in tumor cell) is obtained after these nanocapsules are intravenously injected into estradiol-stimulated human breast adenocarcinoma cell line (MCF-7) xenografts. This has led to the development of a novel method for the treatment of hormone-dependent breast cancers.

Thank You. Refer to the class notes for further details.