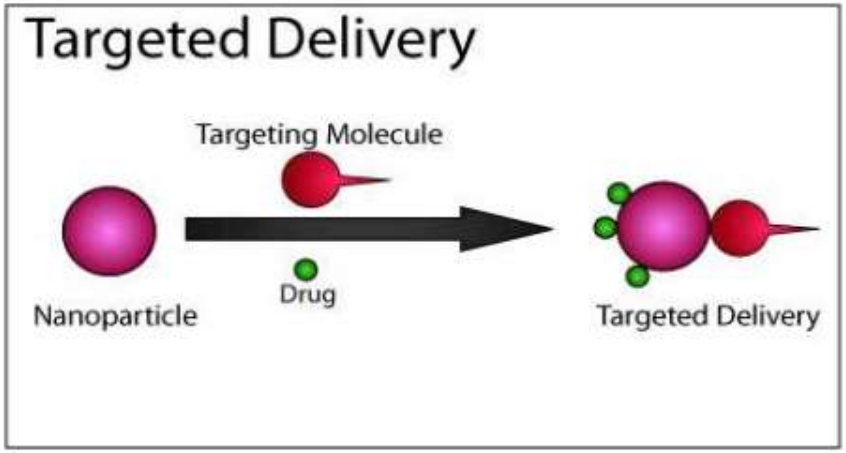

Targeted Drug Delivery
Systems

ON TARGET

SMART DRUG THERAPY???



INDEED[1]..

Agenda

- Introduction
- Advantages and disadvantages
- Types
- Composition
- Biopharmaceutical considerations

- Is a kind of smart DDS.
- It is an advanced method of delivering drugs to the patients in such targeted sequences that increases the concentration of delivered drug to the targeted body part of interest only (**organs/tissues/cells**) which in turn improves efficacy of treatment by reducing side effects of drug administration.

- Products based on such a delivery system are being prepared by considering the specific properties of target cells, nature of markers or transport carriers or vehicles which convey drug to specific receptors and ligands and physically modulated components.

Research in the field of targeted drug delivery has given several options of carrying out the above functions:

- Direct targeting to site of action, e.g., direct injection, catheter, topical applications for skin diseases.
- Use of external stimuli, e.g., ultrasound .

- Chemical modification of the drug.
- Use of nanocarriers like liposomes, polymeric micelles, polymeric nanoparticles, solid lipid nanoparticles which can be functionalized further with attachment of targeting ligands or antibodies.

Q/ Do you know the best one and why?

- Ideally targeted drug delivery systems should be:

1) biochemically inert (non-toxic).
2) non-immunogenic.
3) physically and chemically stable in vivo and in vitro conditions.
4) Of restricted drug distribution.
5) Characterized by controllable and predictable rate of drug release without affecting the drug action.

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Reasons for Site specific delivery of drugs[2]

Pharmaceutical

- Drug instability in conventional dosage form
- Solubility

Biopharmaceutical

- Low absorption
- High-membrane bounding
- Biological instability

Pharmacokinetic / Pharmacodynamic

- Short half-life
- Large volume of distribution
- Low specificity

Clinical

- Low therapeutic index.

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Advantages and Disadvantages

Targeted drug delivery systems

ADVANTAGES

Control of drug delivery on to a particular site or vicinity with predetermined or expected release kinetics

DISADVANTAGES

- Expensive
- Technical skill required
- Stability issues both Chemical and physical biological as well
- Yield comparatively very less

Factors affecting targeting DDS

- The physicochemical properties of carrier (its charge, mol.wt./ size, surface hydrophobicity, and presence of ligands for interaction with surface receptors).
- The nature of endothelial barrier, healthy or non (inflamed, necrotic or tumorous)

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Biological processes and events involved in drug targeting[2]

- Cellular Uptake and Processing
- Transport across the epithelial barrier
- Extravasation
- Lymphatic Uptake

Targeting can be classified into:

1) Passive (physiology-based):

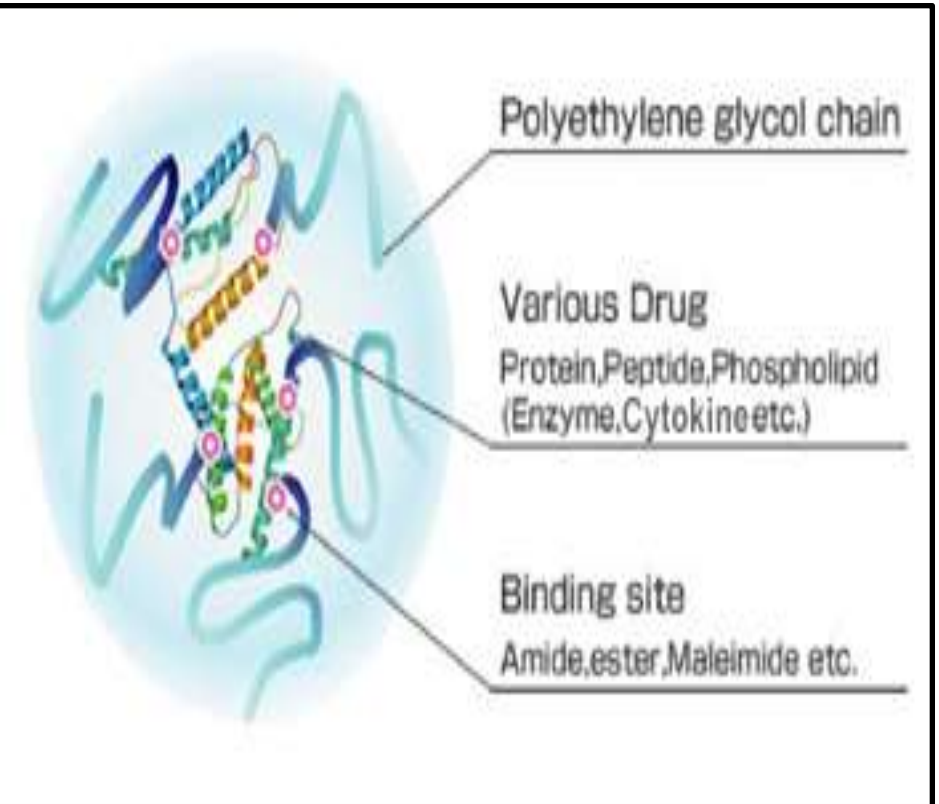
- Is present naturally in the human body.
- Hormones, neurotransmitters, growth factors etc have a natural tendency to go and target the receptors at their sites of action ex. insulin.
- This concept can be applied to the drugs too.
- The accrual of drugs/drug-carrier systems at the intended site of action by the action of physicochemical and physiological factors is passive targeting.

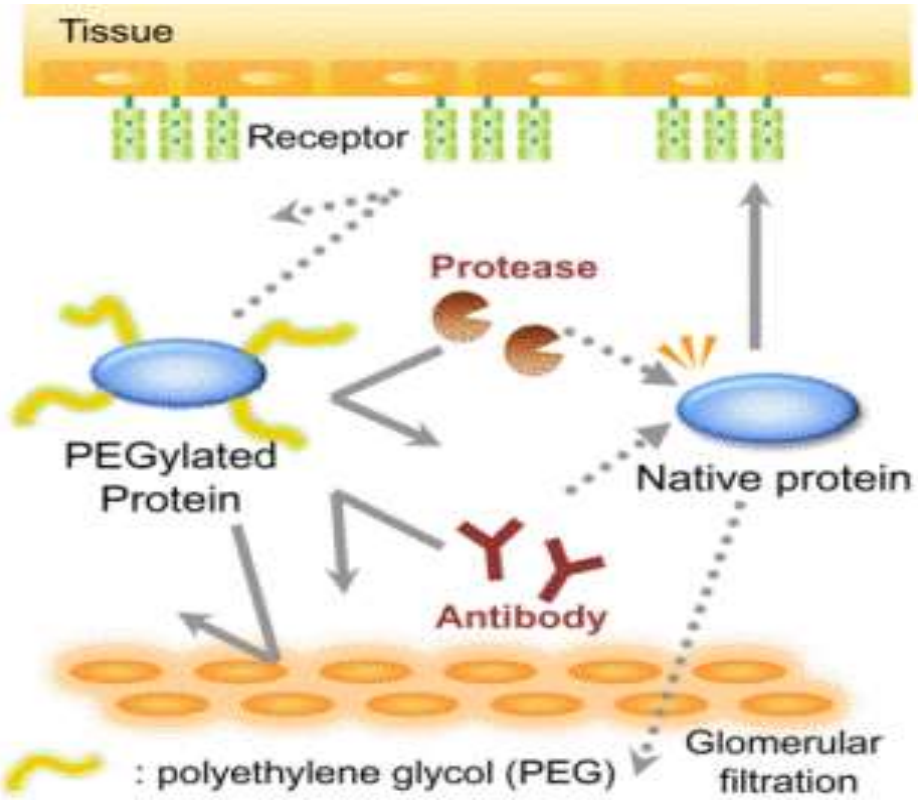
- As physiological factors:

1) Inflammation
2) Tumorous cells
3) Leaky vasculature

- The nanocarriers are largely affected to clearance by the reticulo-endothelial system (RES) comprising of macrophages and mononuclear phagocytes. This fact can be used to passively target the macrophages and even lymph nodes and spleen to treat infections that affect the RES.

- Often modifications (e.g., attachment of polyethylene glycol; PEG= Pegylation) are made on nanocarriers to make them long-circulating, avoiding the RES and granting them time to accumulate at target sites in high amounts (long-circulating nanocarriers)





- Passive targeting also benefits from the presence of internal stimuli, such as pH difference (e.g., low pH in tumor microenvironment), redox systems (e.g., exploiting high glutathione in cancer). Stimuli- sensitive drug targeting systems will be spurred by such stimuli to release the drug only at the target site and spare the normal tissues.

What is the meaning of physical targeting?

2) Active targeting:

- Appropriate modifications and functionalization on the drugs or drug carriers afford them affinity towards specific receptors/markers on cells, tissues or organs.
- Factors such as the disease, the intended target organ, and a larger presence of targetable components on the target organ/cell (e.g., transferrin receptors in tumor) than in normal cells are taken into consideration while deciding on the targeting moiety to be attached to the therapeutic substances.

- Modifications on the drugs or drug carriers can involve the use of ligands such as peptides, antibodies, sugars, lectins, etc.
- Thus, on administration to the body, the targeting moieties will enable the drug/drug-carriers to efficiently reach only the intended sites of action and avoid non specific accumulations and related side effects.

- **This active targeting approach can be further classified into three different levels of targeting which are:**

1) First order targeting refers to restricted distribution of the drug carrier systems to the capillary bed of a predetermined target site, organ or tissue e.g. compartmental targeting in lymphatics, peritoneal cavity, plural cavity, cerebral ventricles, eyes and joints.

2) Second order targeting refers to selective delivery of drugs to specific cell types such as tumour cells and not to the normal cells e.g. selective drug delivery to kupffer cells in the liver.

3) Third order targeting refers to drug delivery specifically to the intracellular site of targeted cells e.g. receptor based ligand mediated entry of a drug complex into a cell by endocytosis

Composition:

- Components of Active-targeted drug delivery (carrier based) are:

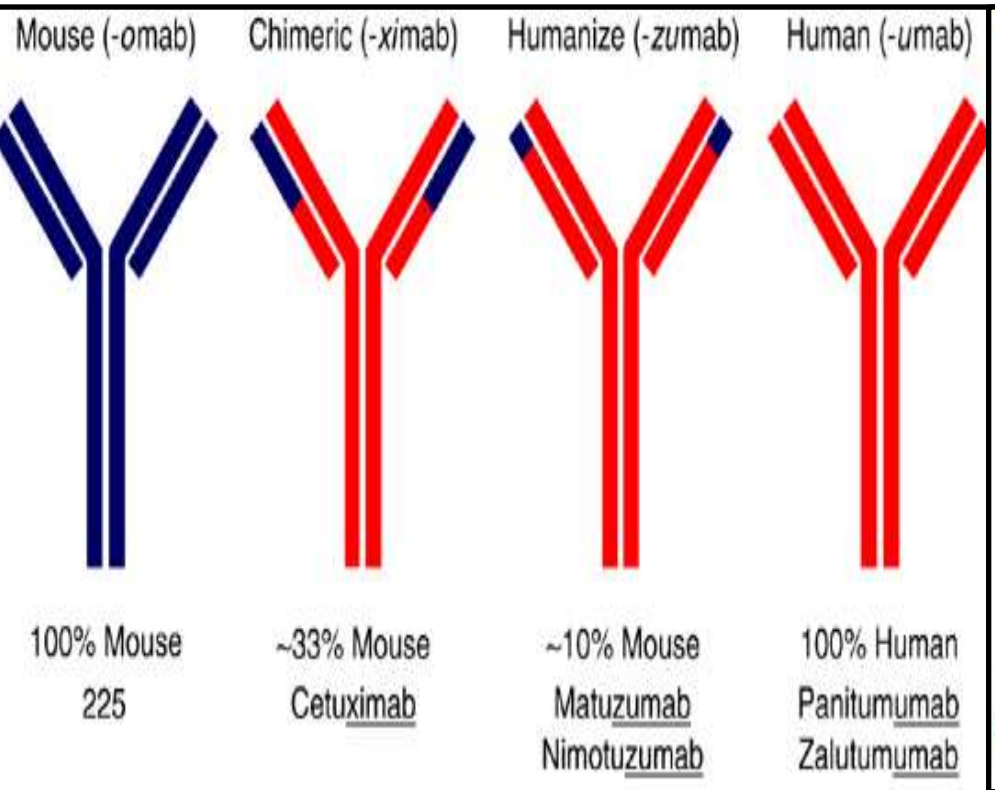
1. An active moiety	For: therapeutic effect
2. A carrier	For: (metabolic) protection, changing the disposition of the drug
3. A homing device	For: specificity, selection of the assigned target site

- Carrier is one of the special molecule or system essentially required for effective transportation of loaded drug up to the pre-selected sites. These 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 delivery vehicles** are also referred as drug vectors which are most important entity required for successful transportation of the loaded drug.
- Drug vectors transports and retains the drug to be delivered it within or in the vicinity of target.

Types of carriers for targeting

- Soluble carrier systems: ex. **MAb** (monoclonal antibodies), Bispecific Ab., modified plasma proteins and soluble synthetic polymers.
- Colloidal particulate carrier systems: Liposomes, bio-degradable nanoparticles, and microspheres



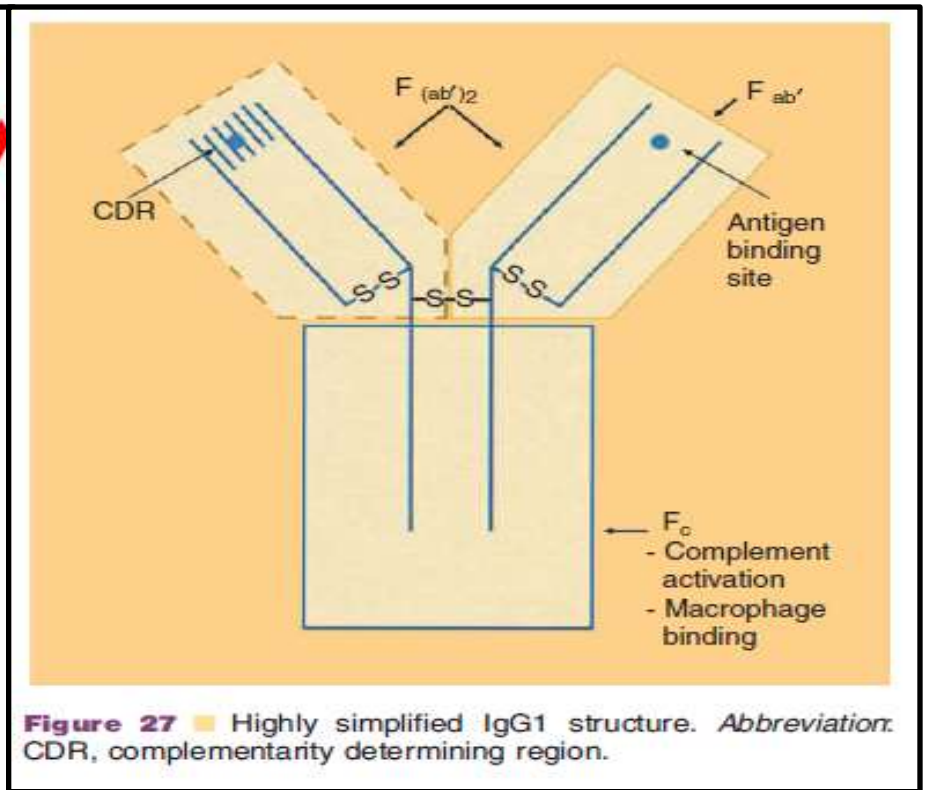
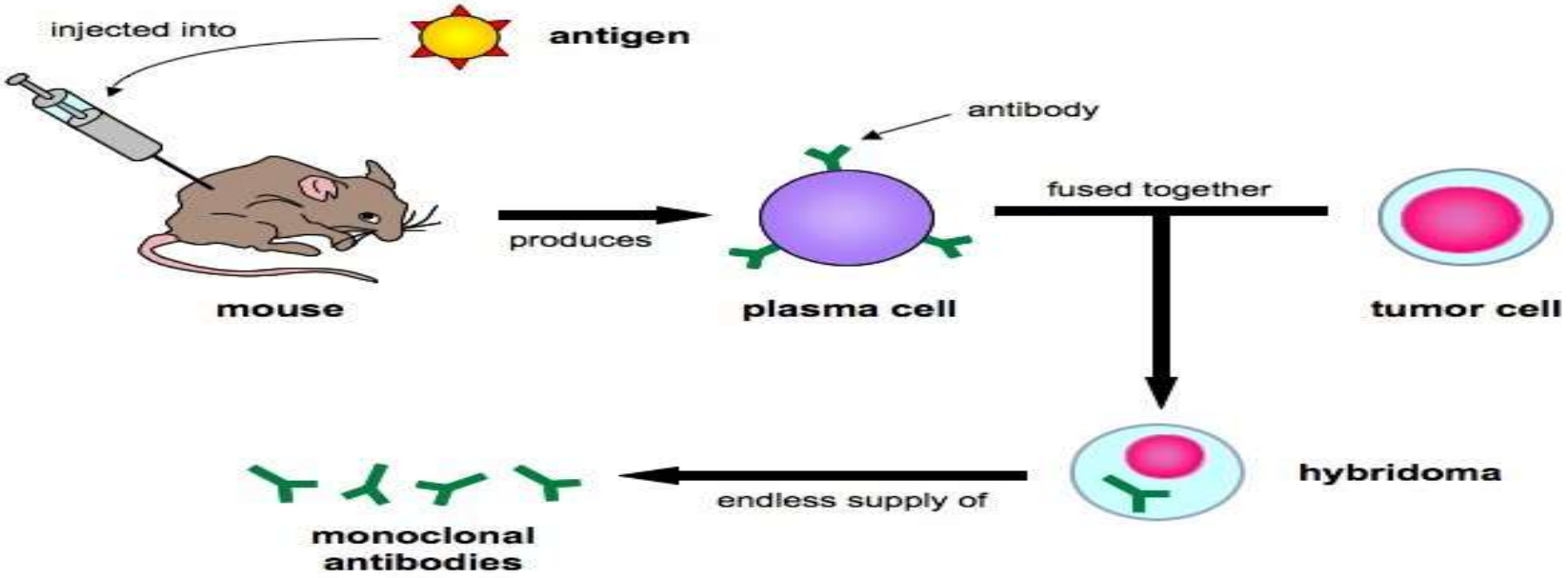
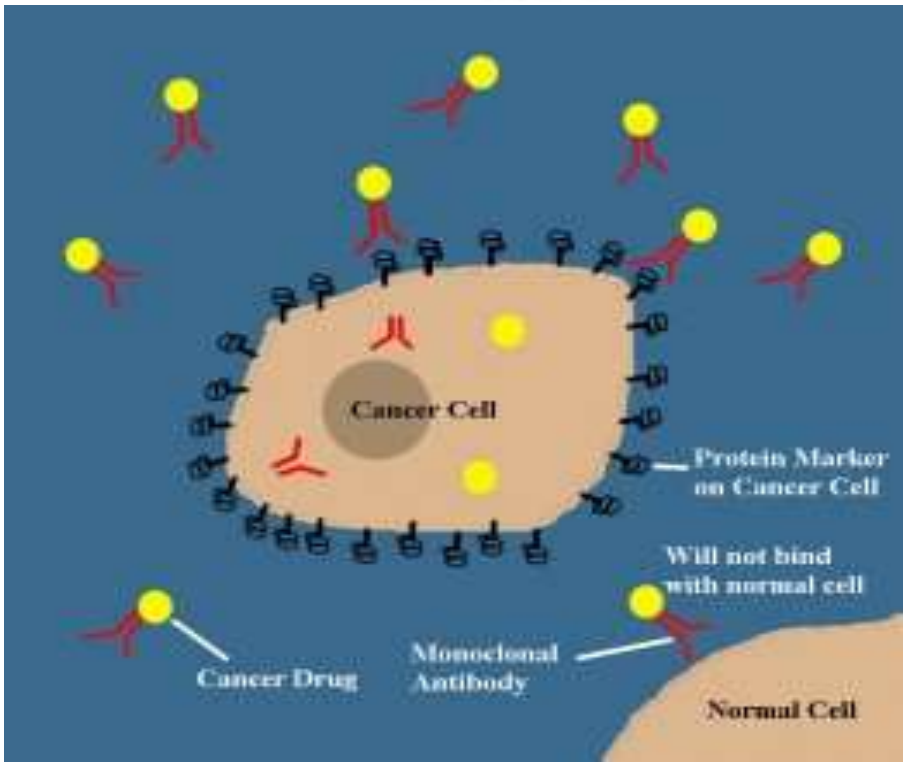
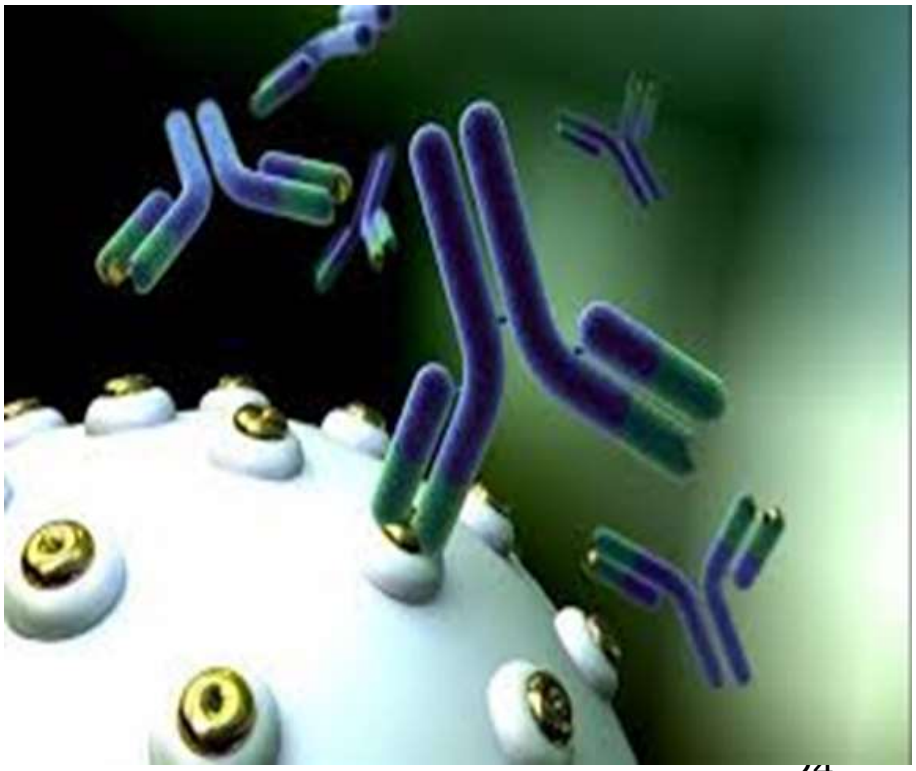


Figure 27 Highly simplified IgG1 structure. *Abbreviation:* CDR, complementarity determining region.


injected into
antigen
antibody
fused together
produces
mouse
plasma cell
tumor cell
hybridoma
endless supply of
monoclonal antibodies

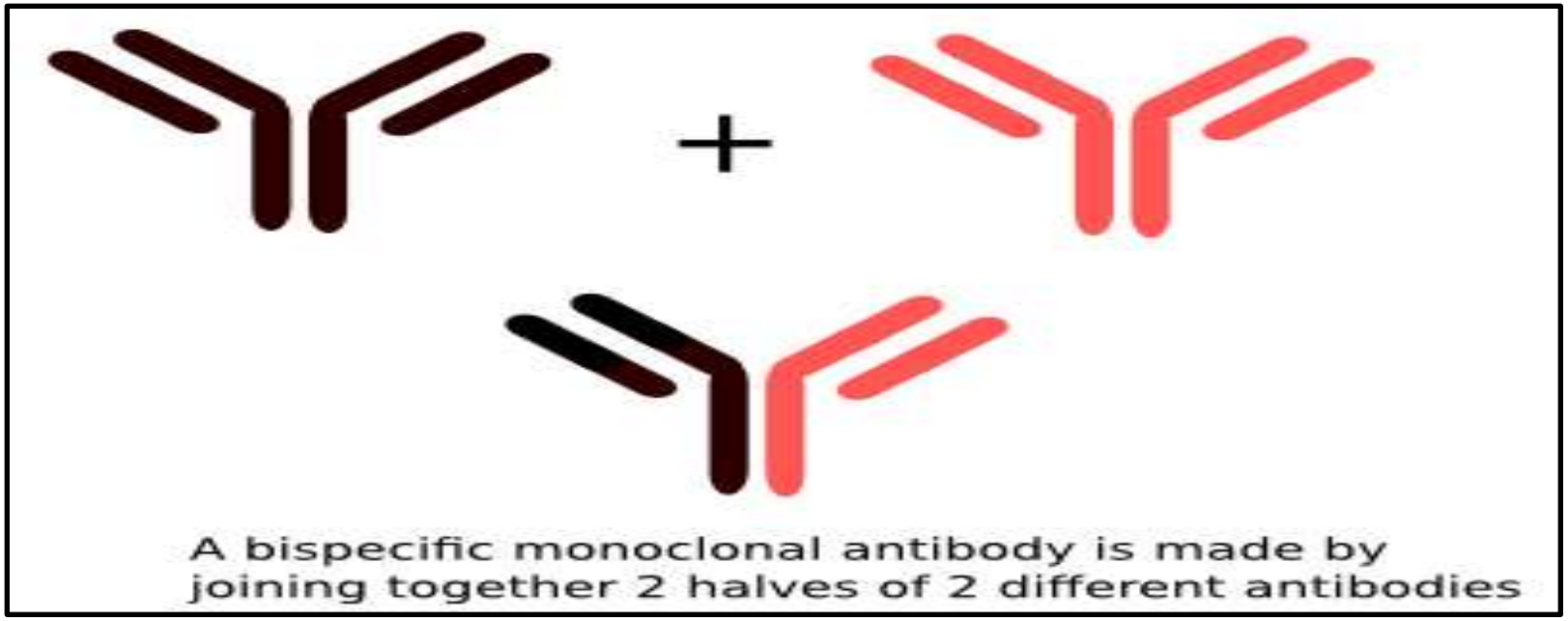

Cancer Cell
Protein Marker on Cancer Cell
Will not bind with normal cell
Cancer Drug
Monoclonal Antibody
Normal Cell



- The majority of strategies based on antigen recognition by antibodies have been developed for more specifically for cancer therapy. These strategies are mostly aimed at tumor associated antigens being present or in more specific term expressed by tumor cells.

- **Antibody-drug conjugates (ADC)** is complex of a drug with a monoclonal antibody which provides selective targeting for tumoral cell masses or lymphomas.
- The drug is released by enzymatic cleavage of the linker under physiological conditions.

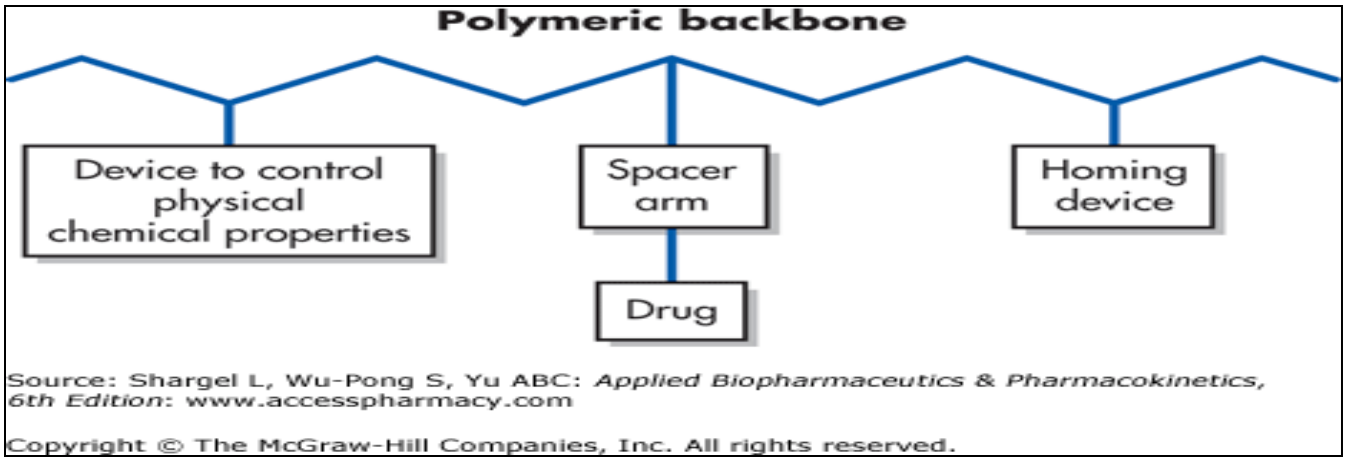
Bispecific MAb



With more therapeutic potential, with two binding sites

- **Modified plasma proteins** can be intelligent drug vehicle for drug transportation due to their solubility and having relatively small molecular weight.
- They can easily be modified by the attachment of different molecules like peptides, sugars, and other ligands to transport the drugs of interest.
- In the case of liver cell targeting, extensive modifications of protein backbones such as albumins have been carried out an effective delivery of the drug.

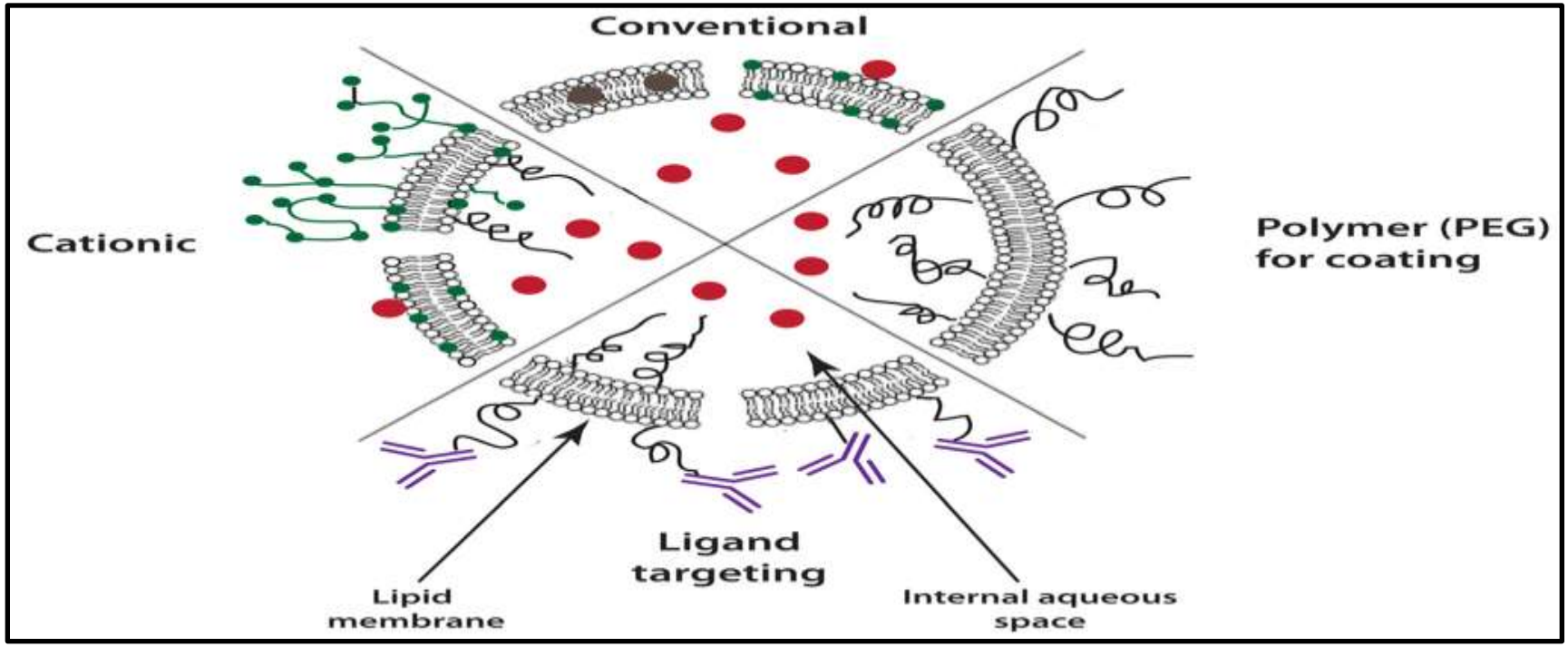
- **Soluble synthetic polymers** have been extensively researched as versatile drug carrier systems.
- Polymer chemistry allows the development of tailor made conjugates in which target moieties as well as drugs can be entrapped into the carrier molecule.
- Examples ????

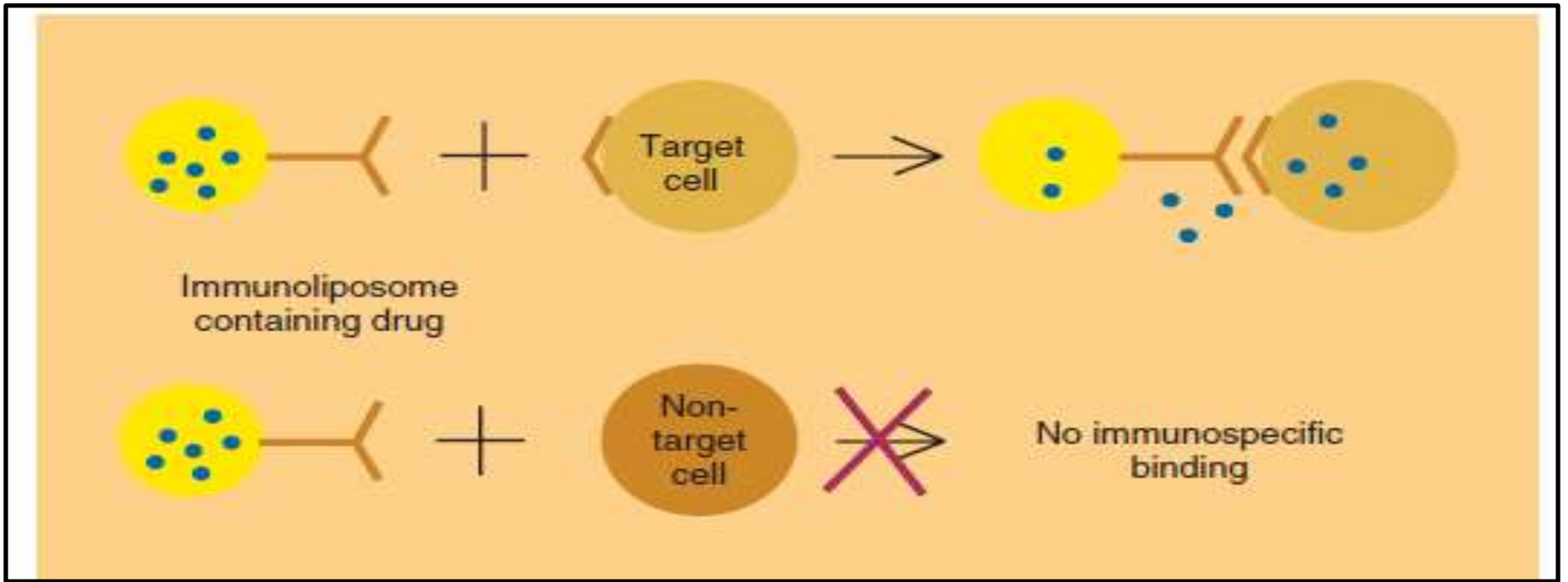


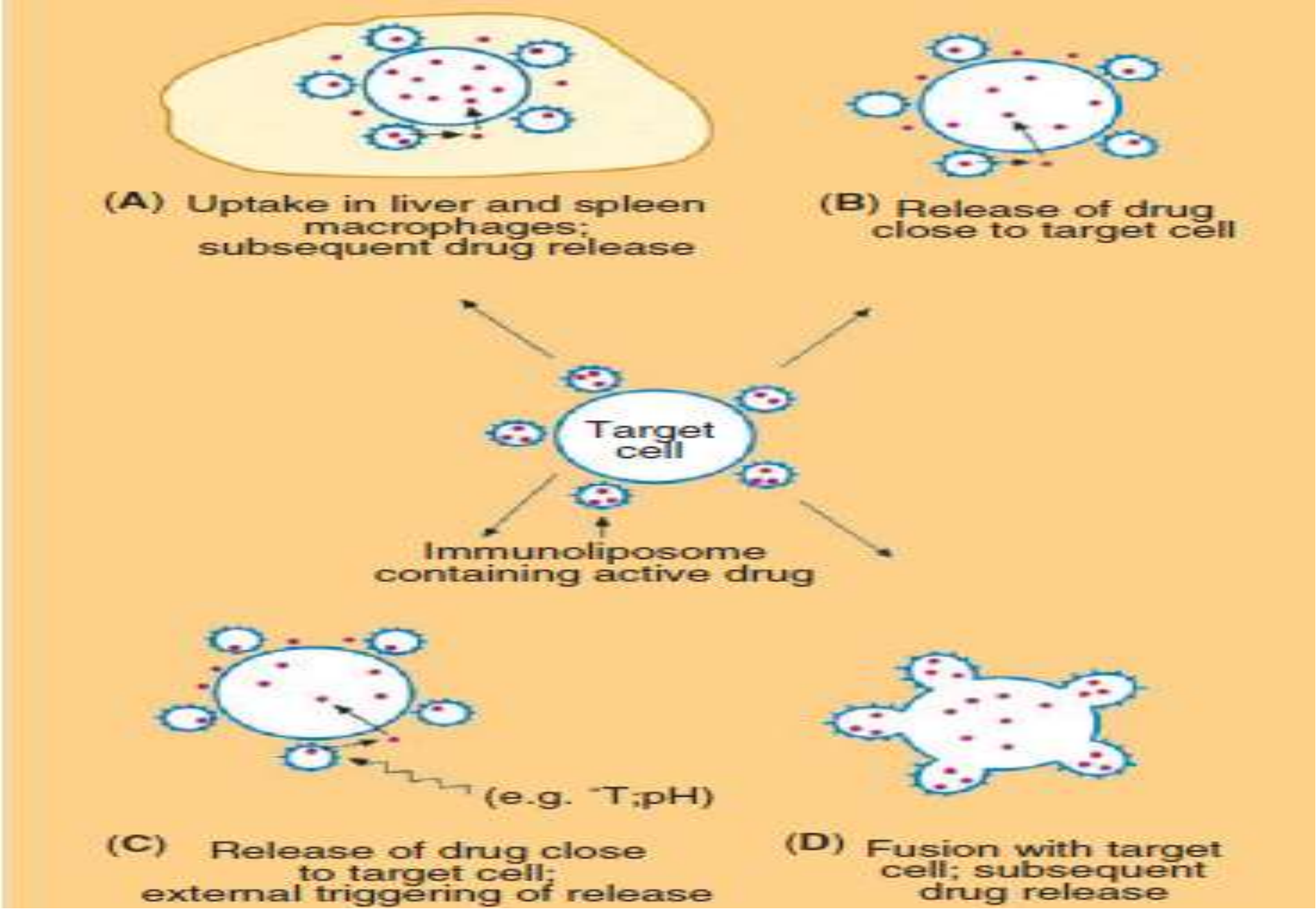
Source: Shargel L, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics, 6th Edition*: www.accesspharmacy.com

- **Liposomes** are small artificially designed vesicles composed of phospholipid bilayers with the size ranging from 20 to 10 000 nm.

- Many liposome formulations are rapidly taken up by macrophages and this can be exploited either for macrophage-specific delivery of drugs or for passive drug targeting which allow slow release of the drug over time from these cells into the general circulation.


Conventional
Cationic
Polymer (PEG)
for coating
Ligand
targeting
Lipid
membrane
Internal aqueous
space


Target
cell
Immunoliposome
containing drug
Non-
target
cell
No immunospecific
binding



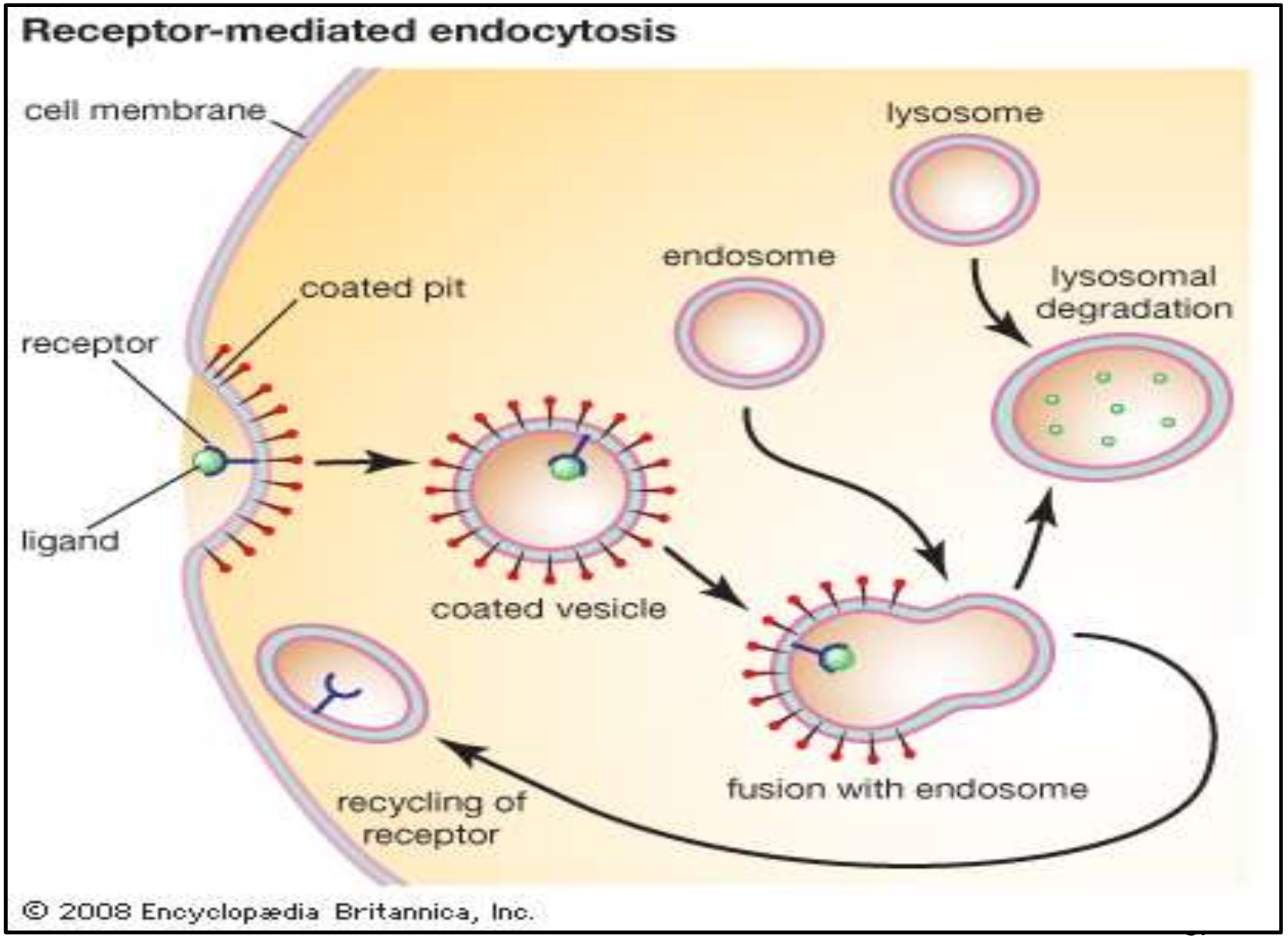
Pathways of drug release in immuno-liposomes

- **Lipid particles** such as LDL and HDL containing a lipid and an apoprotein moiety is termed as natural targeted liposomes and its core can be used to incorporate lipophilic drugs or lipophilic pro-drugs and it does not require covalent bonding with the drug.

- **Microspheres and nanoparticles** consist of biocompatible polymers and belong either to the soluble or the particle type carriers. HPMA (hydroxypropyl methacrylamide) polymeric backbone carriers have also been prepared using dextrans, sepharose or poly-L-lysine as the main carrier body for the drugs.

- Nanoparticles are smaller (0.2– 0.5 μm) than microspheres (30–200 μm) and may have a smaller drug loading capacity than the soluble polymers.
- Formulation of drugs into the nanoparticles can occur at the surface of the particles and in nucleus, depending on the physicochemical characteristics of the drug.

- The site of drug incorporation significantly affects its release rate from the particle.
- After systemic administration or transportation, they quickly distribute to the target site and subsequently become internalized by the cells of the phagocytic system.


Receptor-mediated endocytosis
cell membrane
lysosome
endosome
lysosomal degradation
coated pit
receptor
ligand
coated vesicle
recycling of receptor
fusion with endosome
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See some movies for further understanding??