Faculty of Pharmacy
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DRUG TARGETING

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DRUG TARGETING

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INTRODUCTION

- The main problem's currently associated with systemic drug administration are:

1. Even bio distribution of pharmaceutical's throughout the body.
2. The lack of drug specific affinity towards a pathological site.
3. The necessity of a large total dose of a drug.
4. Non-specific toxicity and other adverse side effects.

INTRODUCTION

Drug targeting may resolve these problems.

Important terms

- TARGET:

A cell or group of cells in minority, identified to be in need of treatment.

- CARRIERS OR MARKERS:

Carrier is one of the important entity essentially required for effective transportation of loaded drugs.

They are vectors, which sequester, retain drug and transport or deliver it into the vicinity of the target cells.

Important terms

- LIGANDS:

The ligands confer recognition and specificity

upon carrier/vector and lend them to approach the

respective target and deliver the drug.

Ex: antibodies, polypeptides, endogenous hormones etc.

Targeted Drug Delivery System

- A special form of drug delivery system where the pharmacologically active agent or medicament is selectively targeted or delivered only to its site of action or absorption and not to the non-target organs or tissues or cells.

Targeted Drug Delivery System

- Targeted drug delivery implies for selective and effective localization of pharmacologically active moiety at preidentified (preselected) target in therapeutic concentration.
- Thus:

✓ Minimizing toxic effects.

✓ Maximizing therapeutic index.

Advantages Of Drug Targeting

Drug administration protocol maybe simplified.

Drug quantity maybe greatly reduced as will as the cost of therapy.

Drug concentration in the required sites can be sharply increased without side effects.

Ideal Characteristics

Targeted drug delivery system should be:

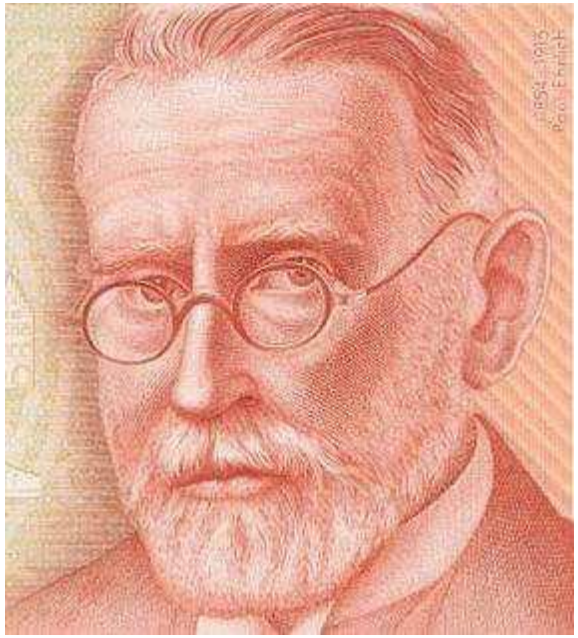
- biochemically inert (non-toxic), nonimmunogenic.
- Both physically and chemically stable in vivo and in vitro.
- Restrict drug distribution to target cells or tissues or organs and should have uniform capillary distribution.
- Controllable and predictable rate of drug release.

Conti……..

- Drug release should not affect the drug action.
- Therapeutic amount of drug release.
- Minimal drug leakage during transit.
- Carriers used must be bio-degradable or readily eliminated from the body without any problem.
- The preparation of the delivery system should be easy or reasonably simple, reproductive and cost effective.

‘Magic Bullet’

CONCEPT OF PAUL EHRLICH (1907)



- Drugs Would Be Targeted By Virtue Of Groups Having Affinity For Specific Cells.
- The concept of magic bullet includes a coordinated behavior of three components:

(a) drug.
(b) targeting moiety.
(c) pharmaceutical carrier.

Carriers

- Most important entity required for successful transportation of the loaded drug.
- Drug vectors which, transport and retain drug; deliver it within or in the vicinity of target.
- Do so through an inherent characteristic or acquired through structural modification.

Properties of an Ideal Drug Carrier

- It must be able to cross anatomical barriers and in case of tumour chemotherapy tumour vasculature.
- It must be recognized specifically and selectively by the target cells and must maintain the specificity of the surface ligands.
- The linkage of the drug and the directing unit (ligand) should be stable in plasma, interstitial and other biofluids.

Properties Of An Ideal Drug Carrier

- Carrier should be non-toxic, non-immunogenic and biodegradable particulate or macromolecule.
- After recognition and internalization, the carrier system should release the drug moiety inside the target organs, tissues or cells.

Types of carriers

Based on the nature of their origin:

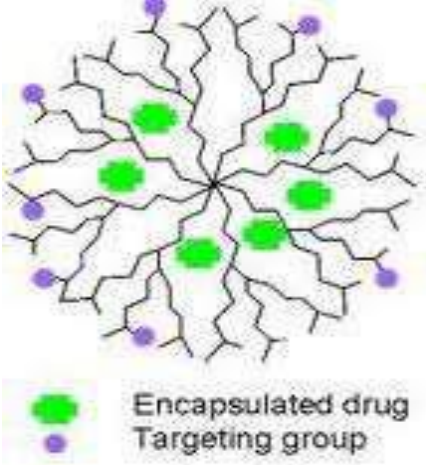
Endogenous

- LDL ,
- HDL
- Chylomicrons,
- Serum albumin,
- Erythrocytes.

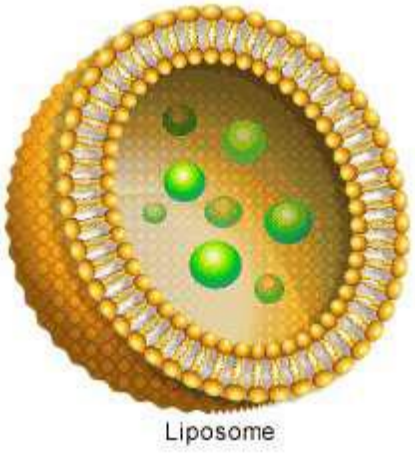
Exogenous

- Microparticulates,
- Soluble polymeric ,
- Biodegradable polymeric drug carriers.

Microspheres



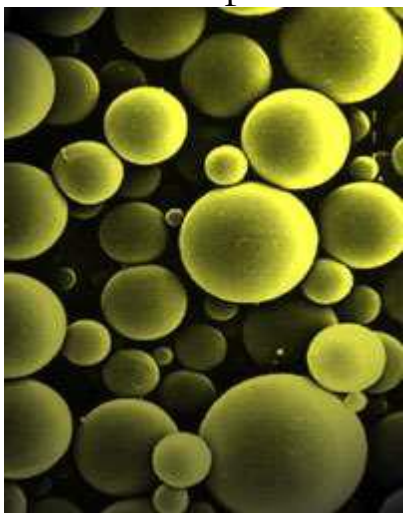
Dendrimers



Pharmaceutical Carriers

Resealed Erythrocytes

Nanoparticles

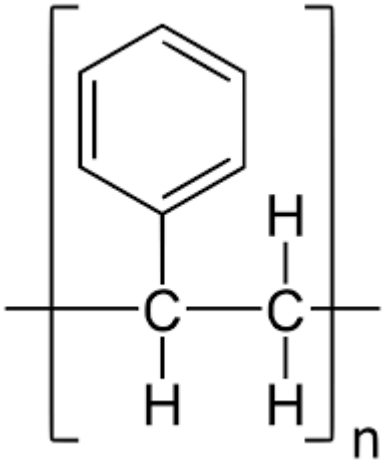


Quantum Dots

- Microspheres :

are characteristically free flowing powders consisting of proteins or synthetic polymers, which are biodegradable in nature and ideally having a particle size 1-1000µm.

Ex: **Polyethylene, polystyrene, poly-d,l-lactide-co-glycolide (PLGA) microspheres**



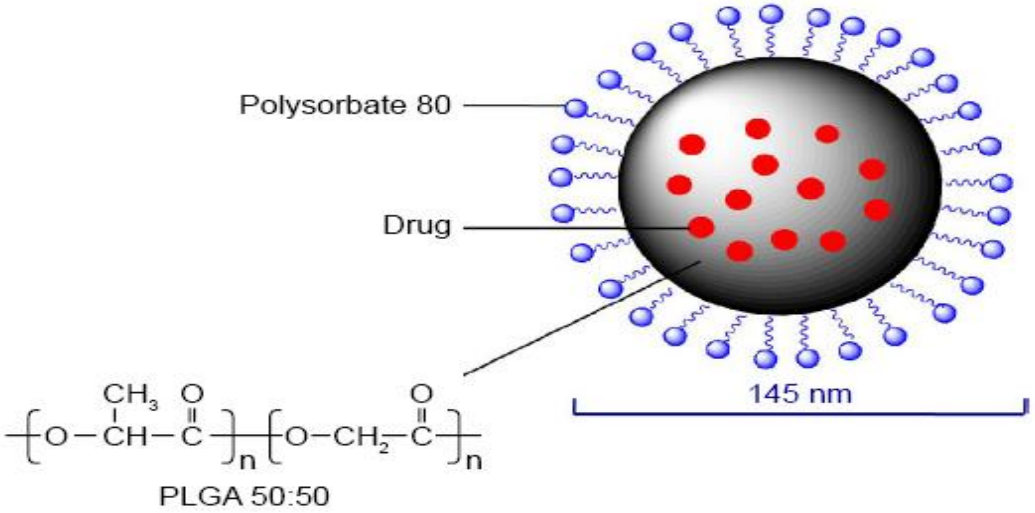
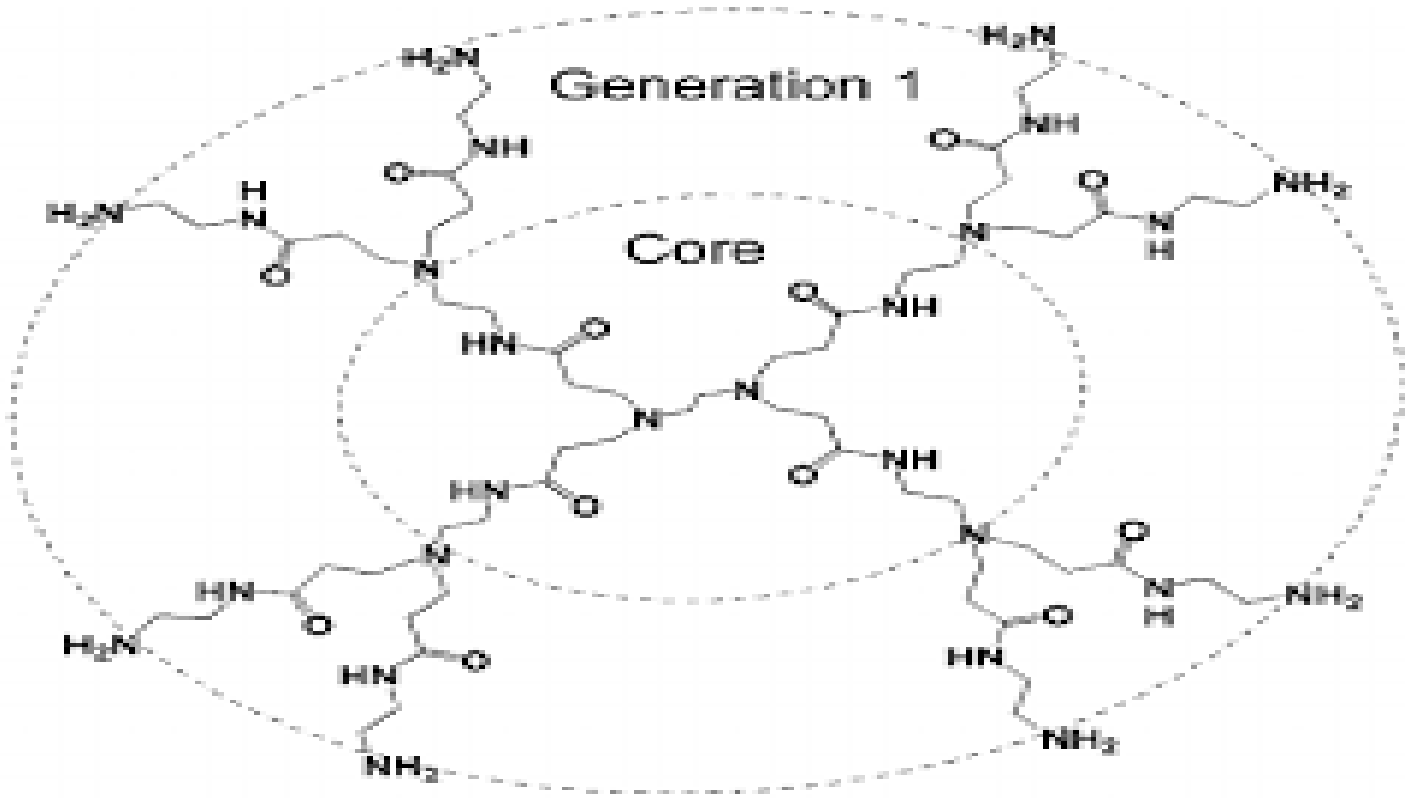


Figure 2 Schematic diagram of the AP-PLGA-NPs.
Abbreviations: AP, acetylpuerarin; PLGA, poly(lactide-*co*-glycolide); NPs, nanoparticles.

- Dendrimers

are highly branched macromolecules

Ex: poly(amidoamine) (PAMAM) dendrimers



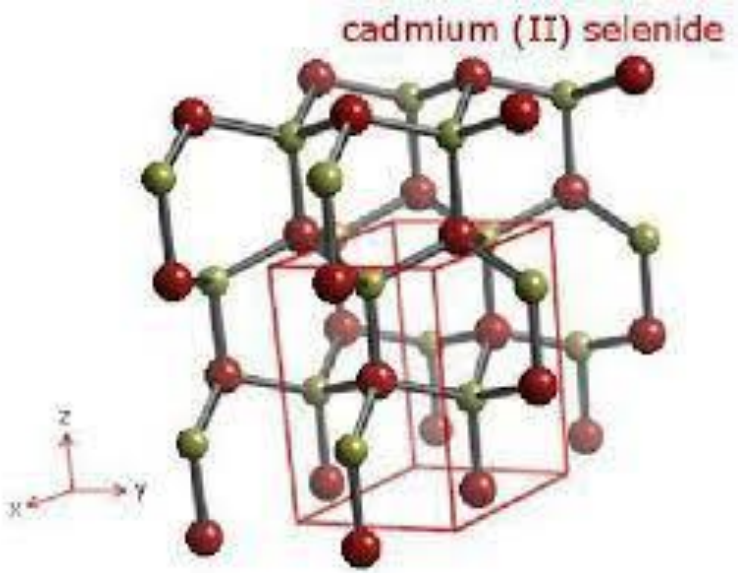
- Erythrocytes

are biocompatible, biodegradable, possess very long circulation half-lives and can be loaded with a variety of chemically and biologically active compounds using various chemical and physical methods

- Quantum Dots:

QDs are very small semiconductor particles, only several nanometres in size.

Ex: cadmium selenide (CdSe)

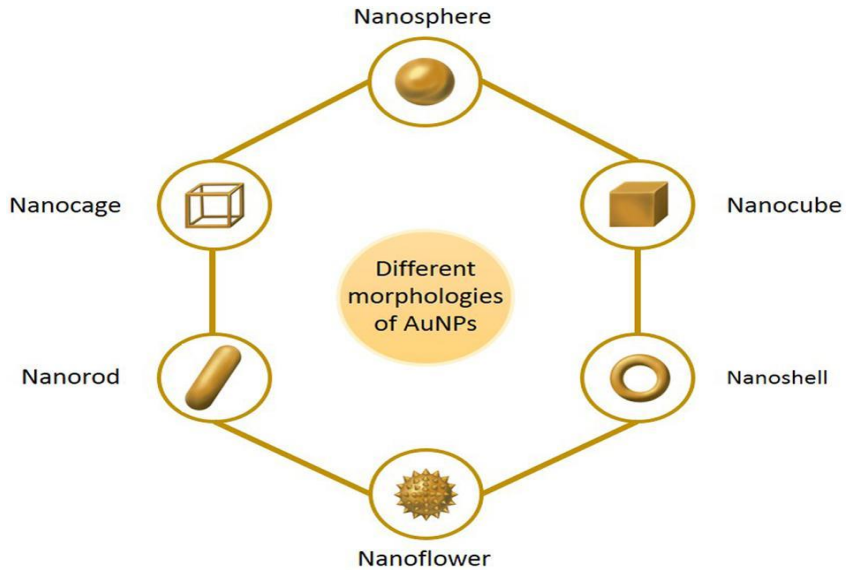


- Nanoparticles:

are solid, colloidal particles with size range from 10 nm to <1000 nm; however, for nanomedical application, the preferential size is less than 200 nm

- Liposomes:

are nanoscale spherical vesicles composed of phospholipid bilayers



Targeting Moieties

- Antibodies.
- Lectins and other proteins.
- Lipoproteins.
- Hormones.
- Charged molecules.
- Polysaccharides.
- Low-molecular-weight ligands.

LEVELS OF DRUG TARGETING

Passive Targeting

- It utilizes the natural course of biodistribution of the carrier.
- The colloids which are taken up by the reticuloendothelial system (RES) can be ideal vectors for passive targeting of drugs to RES predominant compartments.

Distribution of the carrier:

- Passive capture of colloidal carriers by macrophages offers therapeutic opportunities for the delivery of anti-infective agents.

Passive Targeting

- Systems that target the systemic circulation.
- Devices include- drug bearing bilayer vesicular systems

as well as cellular carriers of micron or submicron size range.

Inverse Targeting

- It is a result of the avoidance of passive uptake of colloidal carriers by the RES.
- It can be achieved by suppressing the function of RES by pre-junction of a large amount of blank colloidal carriers or macromolecules like dextran sulphate.
- Based on attempts to circumvent and avoid passive uptake of colloidal carriers by RES leading to reversion of bio distribution trend of the carrier.

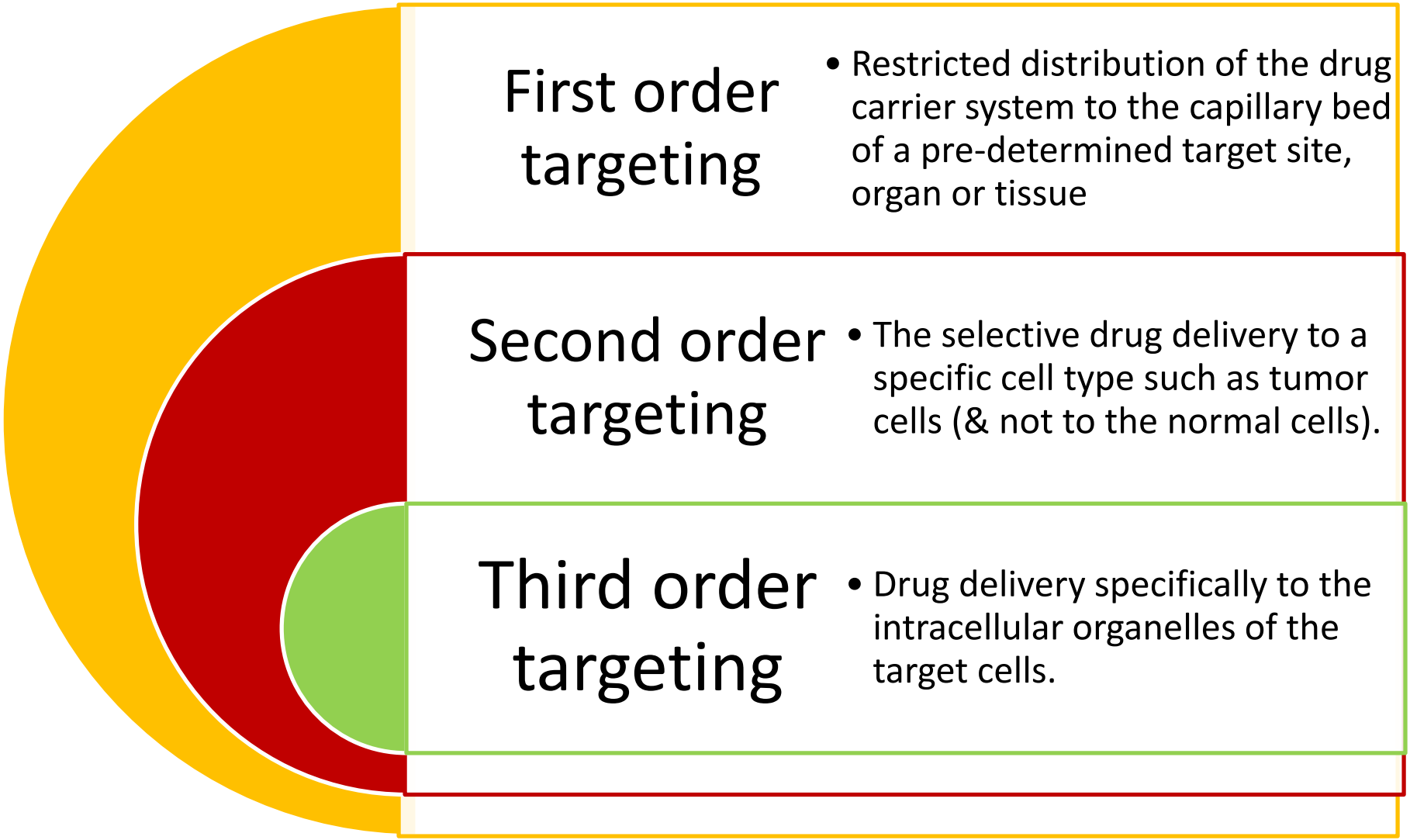
Inverse Targeting

- PEGylated lipid nanoparticle with nearly complete charge shielding for Small interfering siRNA delivery into solid tumors
- Other strategies include modification and defined manipulation of the size, surface charge, composition, surface rigidity & hydrophilicity. characteristics of carriers for desirable biofate.

ACTIVE TARGETING

- It involves the modification or functionalization of the drug carriers so that the contents are delivered exclusively to the site corresponding to which the carrier is architected.

ACTIVE TARGETING



ACTIVE TARGETING

Ligand-mediated Targeting

- Achieved using specific mechanisms such as receptor dependent uptake of natural LDL particles and synthetic lipid microemulsions of partially reconstituted LDL particles coated with the apoproteins.

Physical targeting (Triggered Release)

- The drug delivery programmed and monitored at the external level (ex vivo) with the help of physical means.
- Temperature sensitive liposomes.

DUAL TARGETING

- In this targeting approach, carrier molecule, itself have their own therapeutic activity and thus increase the therapeutic effect of drug.
- Drug targeting using carrier molecules having intrinsic antiviral effect thus synergies the antiviral effect of the loaded active drug.
- Based on this approach, drug conjugates can be prepared with fortified activity profile against the viral replication.

DUAL TARGETING

- Advantages:

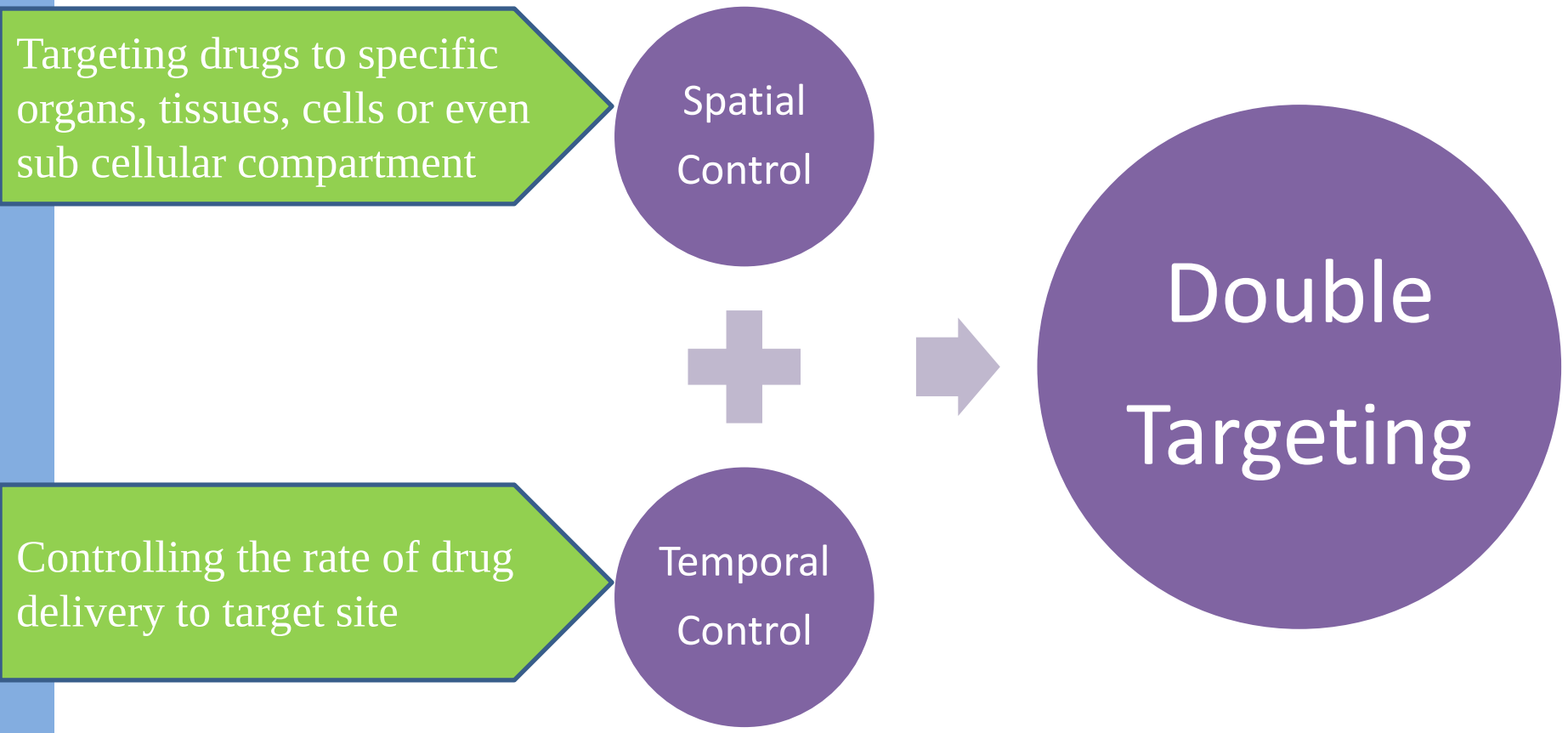
The virus replication process can be attacked at multiple points,

excluding the possibilities of resistant viral strain development.

Double Targeting

- In order to achieve a double targeting effect, site specificity of the drug, by virtue of targeting moiety, a high specificity module (mainly a photosensitizer) is linked to antibodies.

Double Targeting



Combination Targeting

- Suggested by Petit and Gombtz.
- Site-specific delivery of proteins and peptides.
- These targeting systems are equipped with carriers, polymers and homing devices of molecular specificity that could provide a direct approach to target site.

combinations of novel anticancer agents

Overlapping mechanisms	Example drug combination	Toxicities (grade 3–4)	Comment
Toxicity of the combination is predominantly attributable to one drug in the combination	Everolimus + exemestane	Stomatitis, rash, fatigue, and diarrhoea	Toxicity attributable to everolimus makes the combination treatment more toxic than aromatase-inhibitor therapy alone
Overlapping toxicity of the combination is attributable to both drugs	MEK inhibitor + AKT inhibitor	Skin rash and diarrhoea	Overlapping toxicity of each drug
Significant non-overlapping toxicity in addition to overlapping toxicity	lpilimumab + nivolumab	Transaminitis	Unusual with either drug, but significantly more common with the combination therapy
		Diarrhoea, fatigue, rash	Seen with both drugs but additive or greater than additive with the combination treatment
Significant non-overlapping toxicity and overlapping toxicity, and also reduction of certain toxicities	BRAF inhibitor + MEK inhibitor	Pyrexia	Unusual with either drug, but significantly more common with the combination therapy
		Fatigue and diarrhoea	Expected overlapping toxicities
		Keratoaca nthoma/ squamous carcinoma of skin	Incidence lower with the combination therapy compared with BRAF-inhibitor treatment alone

Problems Associated With Targeted Delivery Systems

- Rapid clearance of targeted systems.
- Immune reactions against intravenous administered carrier systems.
- Insufficient localization of targeted systems into tumour cells.
- Diffusion and redistribution of released drugs leading to no specific accumulation.

Gene targeting technology
&
gene therapy of the brain

- Current approach include delivery of the therapeutic gene to the brain by drilling a hole in the head followed by insertion of the gene incorporated in a viral vector.

- The advantage of craniotomy-based gene delivery is that the gene can be expressed in a highly circumscribed area of the brain with an effective treatment volume of 1–10 μl.

Gene targeting technology
&
gene therapy of the brain

- This craniotomy based delivery does not enable the expression of the therapeutic gene widely throughout the brain or even to a relatively localized area such as a brain tumor, which could have a volume greater than several milliliters.

- Viruses have been the vector of choice because the virus-coat proteins trigger endocytosis of the virus into the target brain cell..

Cont…….

- The two most commonly used viral vectors are adenovirus or herpes simplex virus (HSV).
- The problem with both these viruses is that, because they are common, humans have a preexisting immunity.
- This immunity generates an inflammatory response.

Thank You