DRUG TARGETING TO NEOPLASTIC DISEASES

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- **Neoplasm** is an abnormal mass of tissue as a result of **neoplasia**.

- Neoplasia (*new growth* in Greek) is the abnormal proliferation of cells.

- The growth of this clone of cells exceeds, and is uncoordinated with, that of the normal tissues around it.

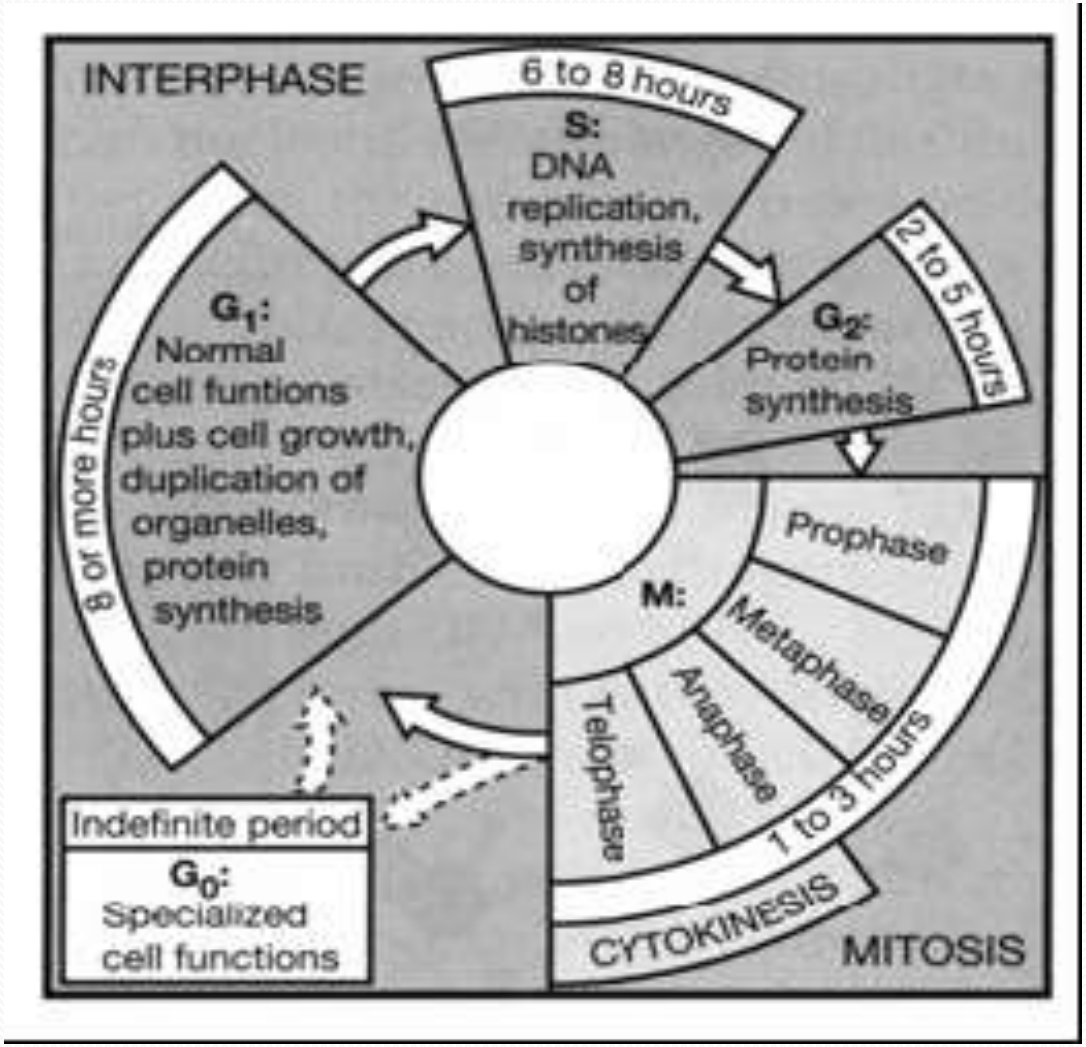
- It usually causes a lump or **tumor**. Neoplasms may be benign, pre-malignant or malignant.

DEFINITION

Neoplasia

- New growth
- Abnormal mass of tissue
- Growth exceeds that of normal tissue
- Growth persists after stimuli initiating it cease
- Tumor = neoplasm

CELL CYCLE OF TUMOR CELL



TYPES OF TUMORS

✓ **BENIGN TUMORS**

- Grow as cohesive, expanding masses that remain localized to site of origin
- Do not have capacity to metastasize to distant sites
- Frequently are surrounded by a fibrous cap

✓ **MALIGNANT TUMORS**

- Grow with progressive infiltration, invasion and destruction of host tissue
- Poorly demarcated from surrounding normal tissue

CARCINOGENESIS/ CAUSES OF CANCER

- Phenotypic level
- Genetic level

Inheritance/ Genotype variation

- BRCA-1 is a gene associated with breast cancer.
- It is a tumor-suppressor gene.

Environmental carcinogens/ phenotype variation

- Ionizing Radiation (U.V., X-rays).
- Organic chemicals: in tobacco smoke, pollutants like asbestos, pesticides.

Viruses:

- Hepatitis B and C viruses (liver cancer).
- Epstein-Barr virus (Burkitt lymphoma & nasalcancer).
- Human papilloma virus (cervical cancer).

HOW CAN YOU DETECT CANCER?

- Change in bowel or bladder habit.
- A sore that does not heal.
- Unusual bleeding.
- Thickening in breast.
- Indigestion or difficulty in swallowing.
- Nagging cough.

PROTECTION AGAINST CANCER

- Low fat diet
- Fruits and vegetables (cabbage), high-fiber foods & food rich in vitamins A and C.
- Avoid. smoking.
- Avoid radiation
- Medical check-up.
- Avoid occupational hazards (asbestos).
- Avoid obesity.
- Avoid smoked foods.
- Sports 30-45 minutes a day.

"TREATMENT FOR TUMOR"

The proposed treatments are:
Surgery.

Chemotherapy.

Radiation therapy.

Steroids for CSF pressure.

Anti-seizure medication.

Spinal tap.

Bone marrow transplantation.

Antibiotics.

Stereo tactic radio surgery.

Gene therapy.

TYPES

- Benign neoplasms include uterine fibroids and melanocytic nevi (skin moles). They do not transform into cancer.

- Potentially malignant neoplasms include carcinoma in situ. They do not invade and destroy but, given enough time, will transform into a cancer.

- Malignant neoplasms are commonly called cancer. They invade and destroy the surrounding tissue, may form metastases and eventually kill the host.

TUMOUR-TARGETED NANOMEDICINES

- Tumour-targeted nanomedicines are drug delivery systems being developed in oncology to improve drug performance by targetting at the right place

Characteristics of An Ideal TUMOUR-TARGETED Nanomedicine

- (1) Increase drug localisation in the tumour through:
  - (a) Passive targeting
  - (b) Active targeting
- (2) Decrease drug localisation in sensitive, non-target tissues
- (3) Ensure minimal drug leakage during transit to target
- (4) Protect the drug from degradation and from premature clearance
- (5) Retain the drug at the target site for the desired period of time
- (6) Facilitate cellular uptake and intracellular trafficking
- (7) Biocompatible and biodegradable

- SITE-SPECIFIC Delivery -aiming for enhanced antitumour activity.

- SITE-AVOIDANCE Delivery -to direct a drug away from those body sites that are particularly sensitive to the toxic effects of the drug

PASSIVE DRUG TARGETING

- Passive targeting refers to the substantial extravasation of the nanomedicine- associated drug into the interstitial fluid at the tumour site,exploiting the locally increased vascular permeability**(enhanced permeation)**
- Solid tumours tend to lack functional lymphatics, and extravasated (nano)materials are retained within the tumour site for prolonged periods of time**(Increased retention)**

✓ This 'enhanced permeability and retention' (EPR) effect is currently the most important strategy for improving the delivery of low-molecular-weight (chemo)therapeutic agents to tumours

LIPOSOMES –PASSIVE TARGETING

- Liposomes are self-assembling colloid structures composed of lipid bilayers surrounding (an) aqueous compartment(s), and can encapsulate a wide variety of (chemo)therapeutic agents.
- Liposomes-phospholipid bilayers
- Stealth liposomes
- Thermosensitive liposomes(that can be triggered to release its contents)

POLYMERS

- Polymeric macromolecules can be conjugated to pharmacologically active agents by means of linkers that are stable in blood, but labile in the acidic and/or enzymatic conditions typical of, for example, the tumour microenvironment or certain intracellular compartments ~

  'Polymer Therapeutics'

- Polymers such as albumin, chitosan, and heparin occur naturally and have been a material of choice for the delivery of oligonucleotides,DNA, and protein, as well as drugs.

- Synthetic polymers such as N-(2-hydroxypropyl)-methacrylamide copolymer (HPMA), polystyrene-maleic anhydride copolymer, polyethylene glycol (PEG), and poly-L-glutamic acid (PGA), PGA was the first biodegradable polymer to be used for conjugate synthesis

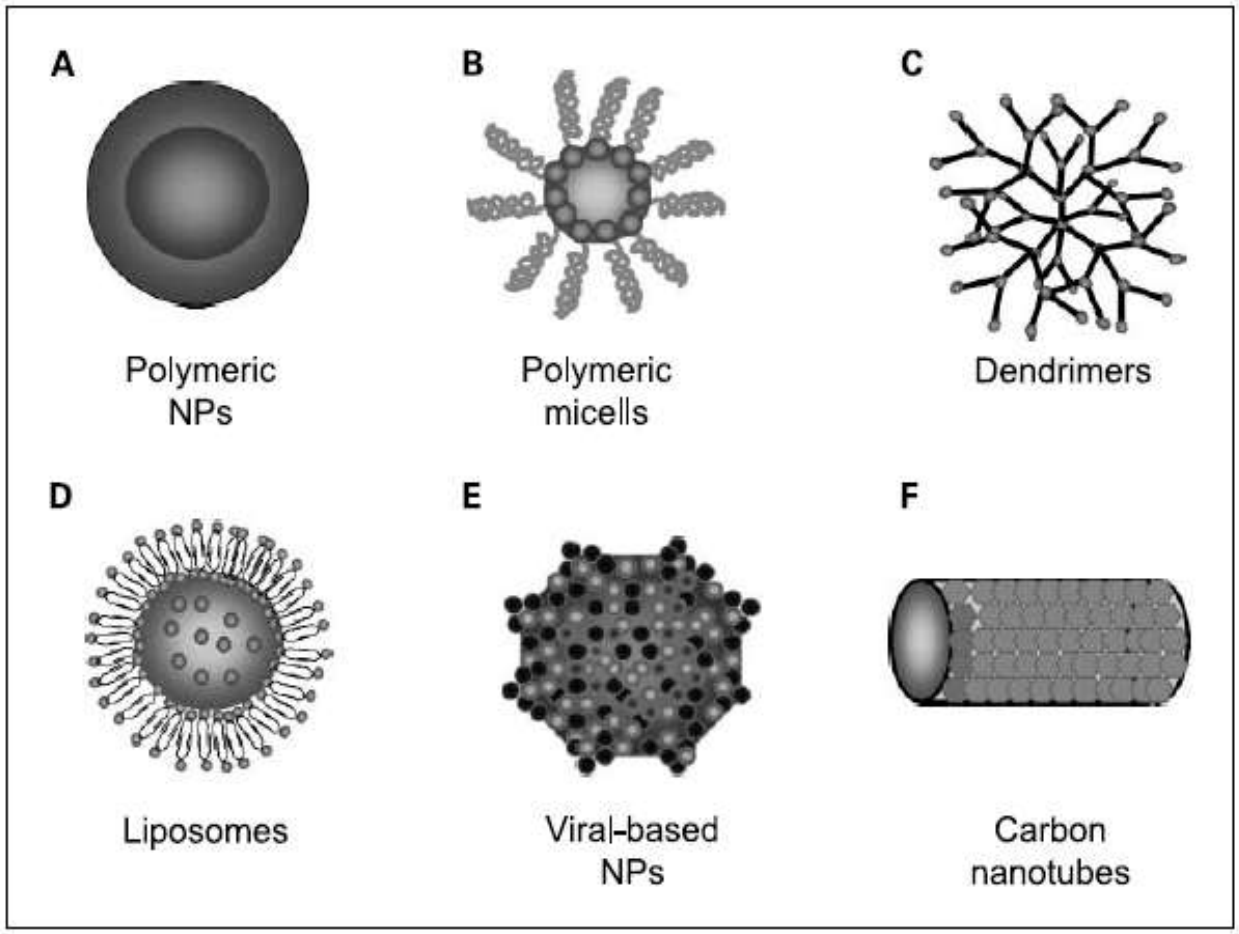


Fig. 1. Types of nanocarriers for drug delivery. *A,* polymeric nanoparticles: polymeric nanoparticles in which drugs are conjugated to or encapsulated in polymers. *B,* polymeric micelles: amphiphilic block copolymers that form to nanosized core/shell structure in aqueous solution. The hydrophobic core region serves as a reservoir for hydrophobic drugs, whereas hydrophilic shell region stabilizes the hydrophobic core and renders the polymer to be water-soluble. *C,* dendrimers: synthetic polymeric macromolecule of nanometer dimensions, which is composed of multiple highly branched monomers that emerge radially from the central core. *D,* liposomes: self-assembling structures composed of lipid bilayers in which an aqueous volume is entirely enclosed by a membranous lipid bilayer. *E,* viral-based nanoparticles: in general structure are the protein cages, which are multivalent, self-assembles structures. *F,* carbon nanotubes: carbon cylinders composed of benzene rings.

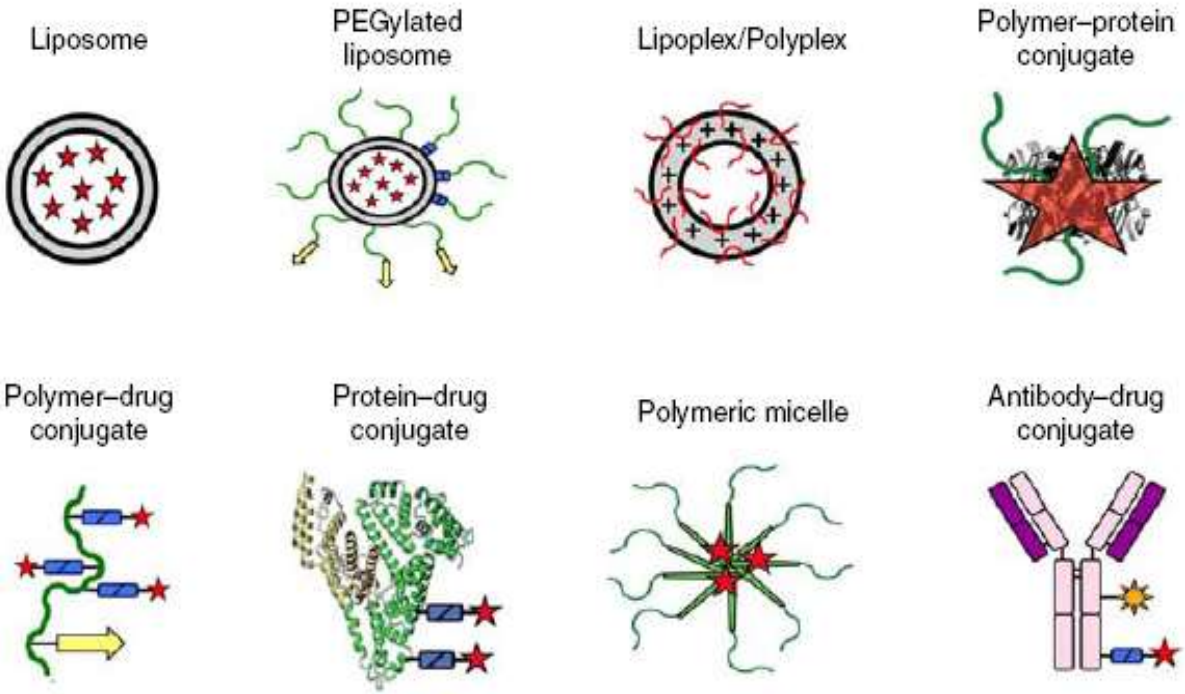


Figure 1 Examples of clinically used tumour-targeted nanomedicines. Representative examples of clinically used tumour-targeted nanomedicines. Liposomal bilayers are depicted in grey, polymers and polymer-coatings in green, biodegradable linkers (for releasing drugs and polymer coatings) in blue, targeting ligands in yellow, antibody fragments in purple, radionuclides in orange and the conjugated or entrapped (chemo)therapeutic agents in red.

Table 2 Examples of clinically used tumour-targeted nanomedicines

Compound	Name	Indication
Liposomal doxorubicin	Myocet, Caelyx (Doxil)	Breast, ovarian, KS
Liposomal daunorubicin	Daunoxome	Kaposi sarcoma
Liposomal vincristine	Onco-TCS	Non-hodgkin lymphoma
Liposomal cisplatin	SPI-77	Lung
Liposomal lurtotecan	OSI-221	Ovarian
Cationic liposomal c-Raf AON	LErafAON	Various
Cationic liposomal E1A pDNA	PLD-E1A	Breast, ovarian
Thermosensitive liposomal doxorubicin	ThermoDox	Breast, liver
Albumin-paclitaxel	Abraxane	Breast
Albumin-methotrexate	MTX-HSA	Kidney
Dextran-doxorubicin	DOX-OXD	Various
PEG-L-asparaginase	Oncaspar	Leukaemia
PEG-IFNα2a/−IFNα2b	PegAsys/PegIntron	Melanoma, leukaemia
PHPMA-doxorubicin	PK1	Breast, lung, colon
Galactosamine-targeted PK1	PK2	Liver
PGA-paclitaxel	Xyotax	Lung, ovarian
Paclitaxel-containing polymeric micelles	Genexol-PM	Breast, lung
Cisplatin-containing polymeric micelles	Nanoplatin	Various
Doxorubicin-containing polymeric micelles	NK911	Various
SN38-containing polymeric micelles	LE-SN38	Colon, colorectal
^{90}Yttrium-Ibritumomab tiuxetan (α-CD20)	Zevalin	Non-hodgkin lymphoma
DTA-IL2 fusion protein (α-CD25)	Ontak	T-cell lymphoma
Ozogamycin-gemtuzumab (α-CD33)	Mylotarg	Leukaemia
Doxorubicin-cBR96 (α-CD174)	SGN-15	Lung, prostate, breast

VIRAL NANOPARTICLES

- A variety of viruses including cowpea mosaic virus, cowpea chlorotic mottle virus, canine parvovirus, and bacteriophages have been developed for biomedical and nanotechnology applications that include tissue targeting and drug delivery.

- They have natural affinity for receptors such as transferrin receptors that are up-regulated on a variety of tumor cells.

CARBON NANOTUBES

- Carbon nanotubes are carbon cylinders composed of benzene rings that have been applied in biology as sensors for detecting DNA and protein, diagnostic devices for the discrimination of different proteins from serum samples, and carriers to deliver vaccine or protein.

- The multiple covalent functionalizations on the sidewall or tips of carbon nanotubes allows them to carry several molecules at once.

ACTIVE DRUG TARGETING

- Targeting ligands are attached to drugs and drug delivery systems to act as homing devices for binding to receptor structures expressed at the target site.

- Antibody–drug conjugates targeted to, for example,CD20, CD25 and CD33, which are (over)expressed in non-Hodgkin's lymphoma, T-cell lymphoma and acute myeloid leukaemia, respectively, have been successfully used for delivering radionuclides (Zevalin), immunotoxins (Ontak) and antitumour antiobiotics (Mylotarg) more selectively to tumour cells

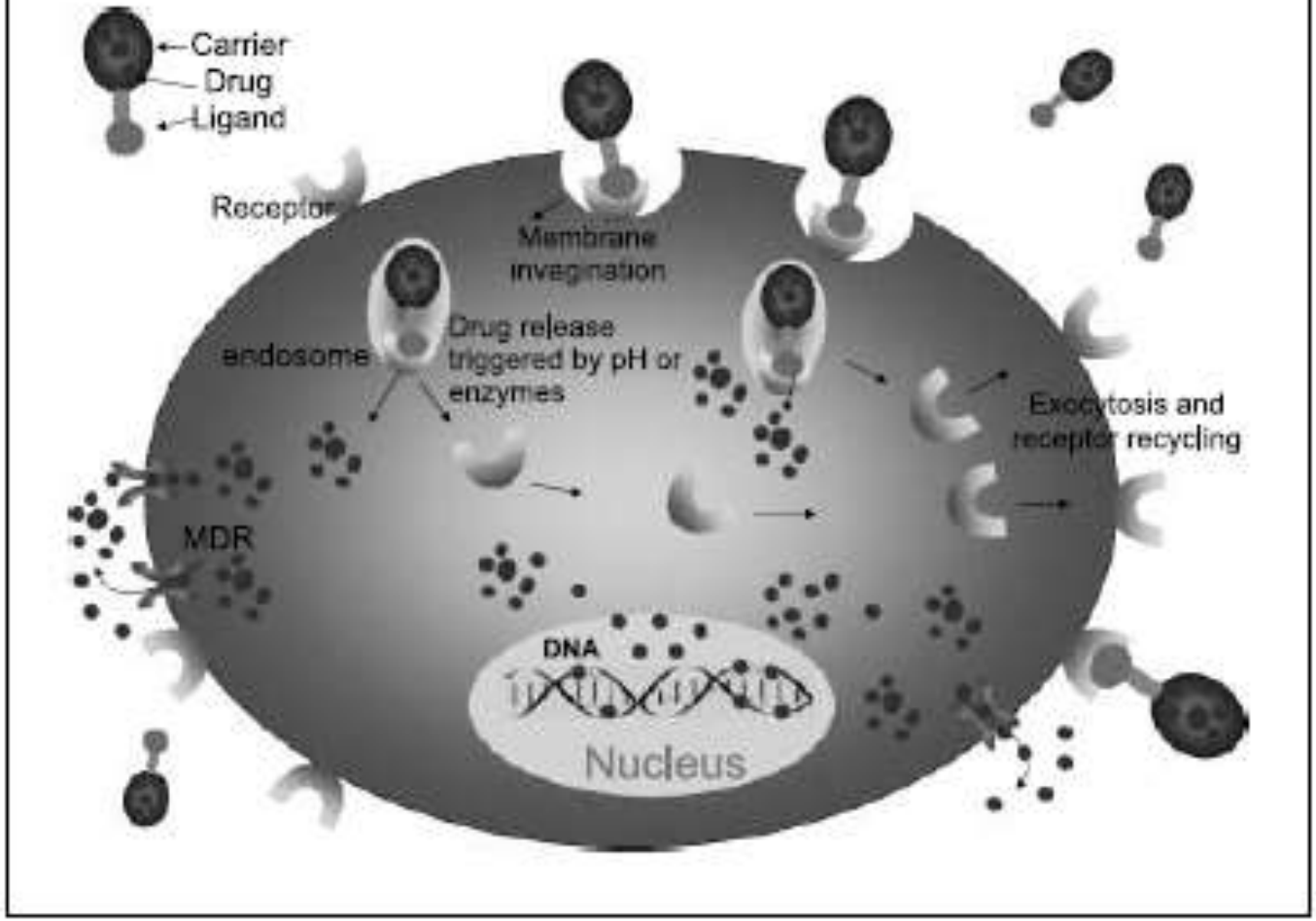


Fig. 3. Internalization of nanoparticles via receptor-mediated endocytosis.

- ✓ Antibodies, antibody fragments and peptides have also been used as targeting moieties for drug delivery systems.

- Examples:Galactosamine-targeted PHPMAdoxorubicin, GAH-targeted Doxorubicin-containing Immunoliposomes

- The folate receptor is a well-known tumor marker that binds vitamin folate and folate-drug conjugates with a high affinity and carries these bound molecules into the cells via receptor mediated endocytosis

- The design of delivery systems targeted to endocytosis-prone surface receptors, such as the transferrin receptor, the folate receptor and EGFR – used for targeting systemic anticancer therapy.

- Aptamers are oligonucleic acids such as DNA or RNA that bear unique three-dimensional conformations capable of binding to target antigens with high affinity and specificity

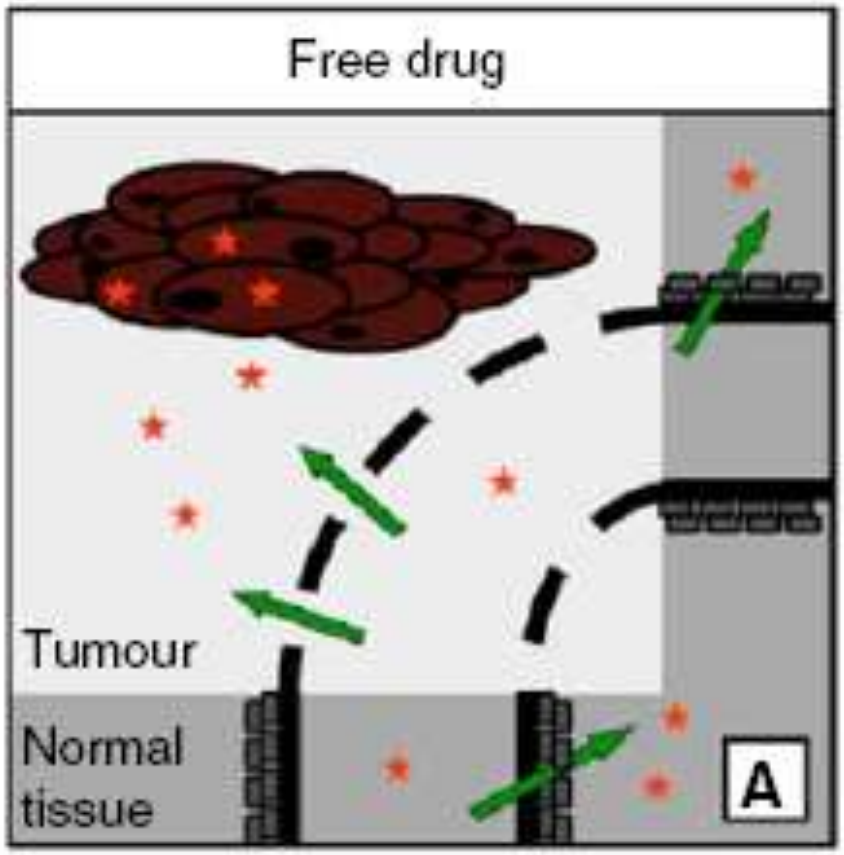
- They have been applied to drug delivery systems as a ligand to enhance selectivity.

- Docetaxel-encapsulated poly(lactic-co-glycolic acid) nanoparticle conjugated with an aptamer to target prostate cancer

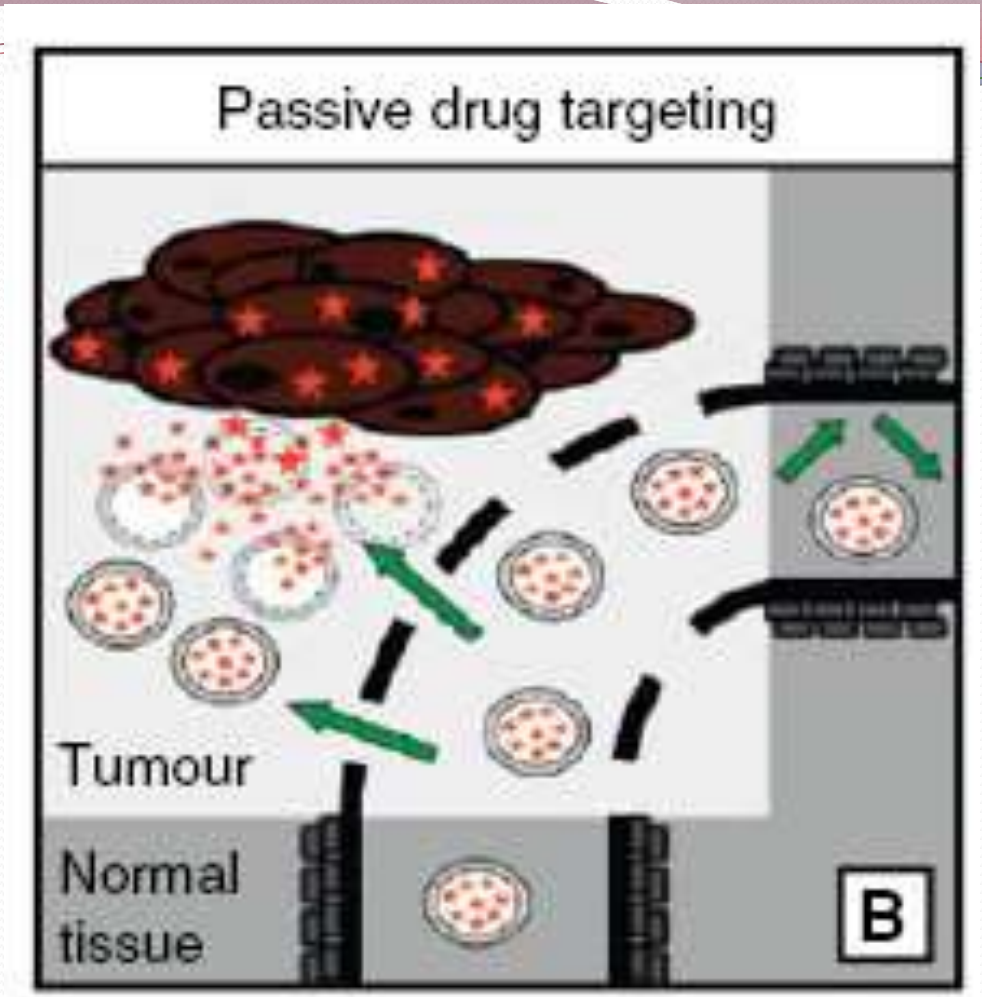
LACK OF OXYGEN

- ✓ Destruction of the endothelium in solid tumours can result in the death of tumour cells induced by the lack of oxygen and nutrients.

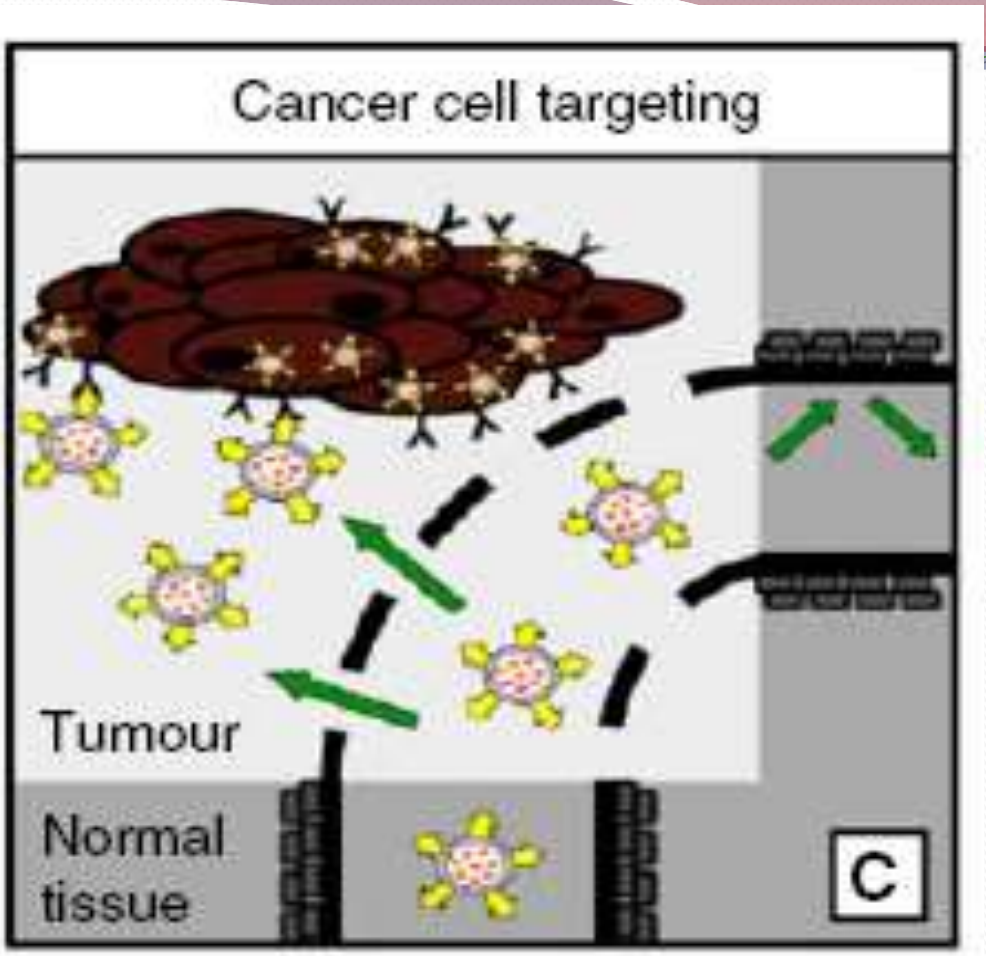
- ✓ This observation, together with the high accessibility of luminal surface receptors, has led to the design of nanomedicines actively targeted to tumour endothelial cells



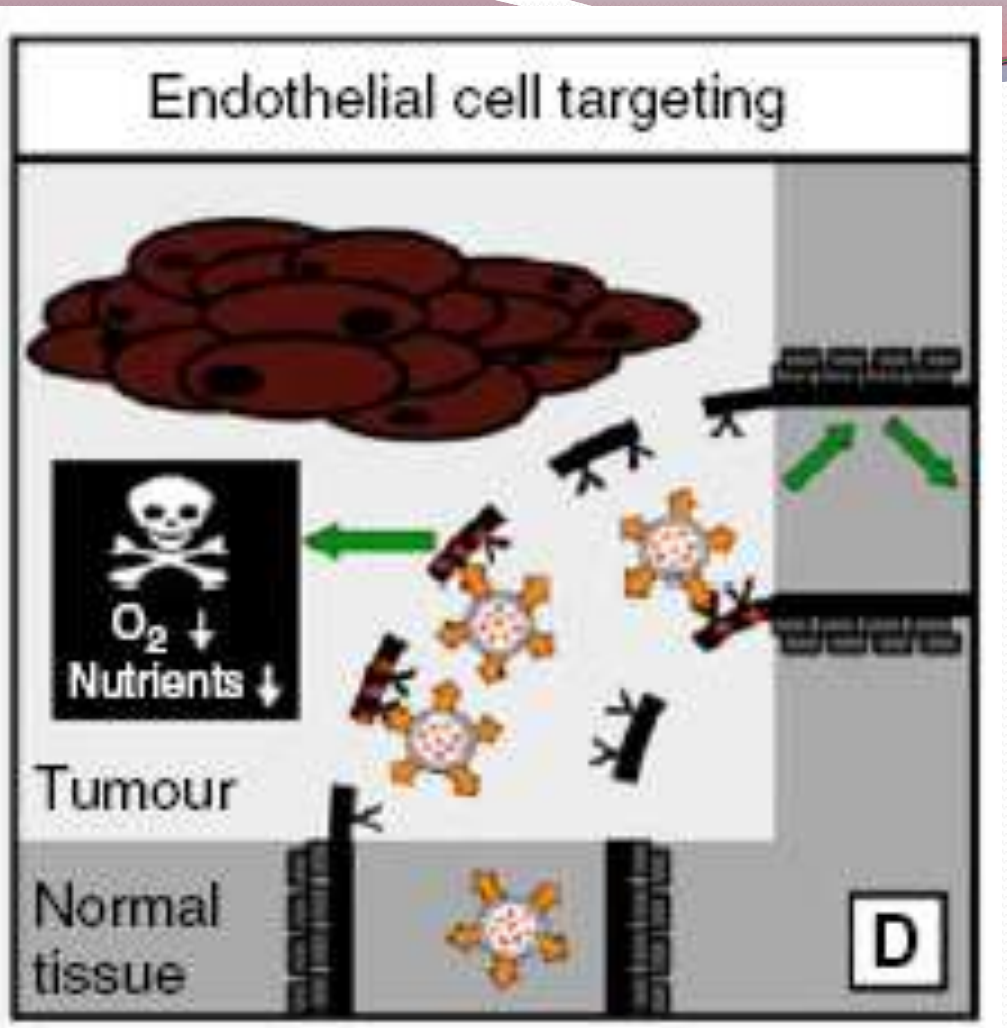
✓Upon the intravenous injection of a low-molecular-weight (chemo)therapeutic agent, which is often rapidly cleared from blood, only low levels of the drug accumulate in tumours and in tumour cells, whereas their localisation to certain healthy organs and tissues can be relatively high.



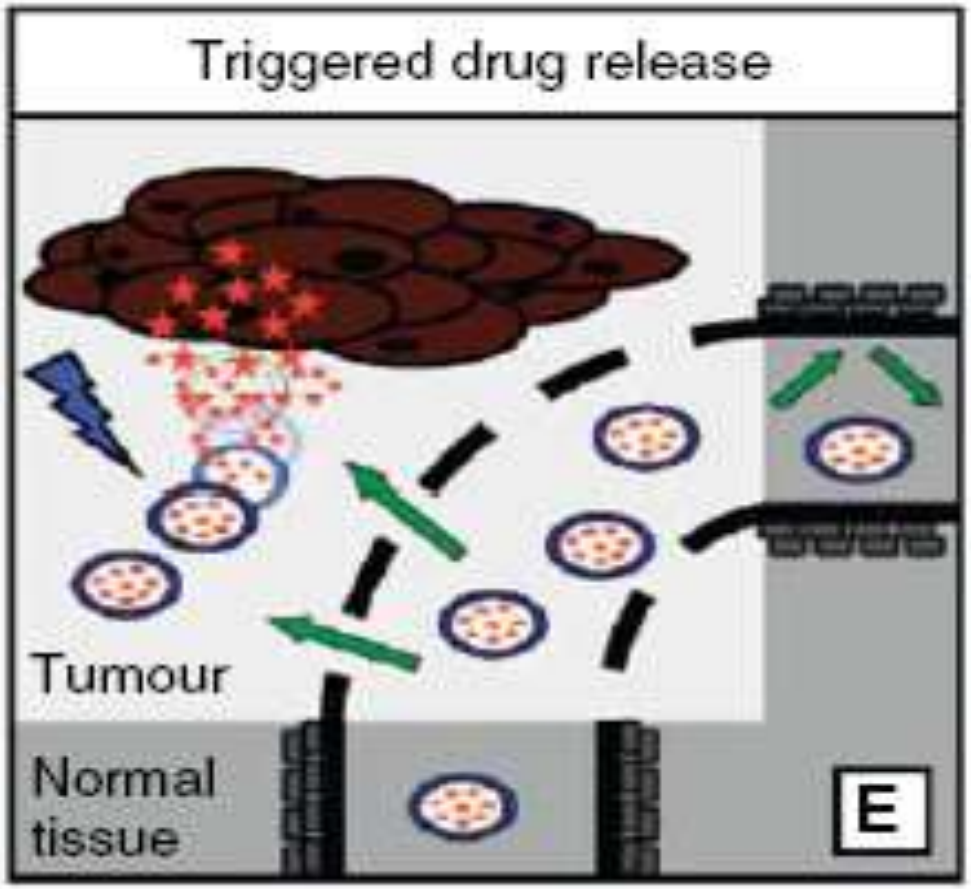
✓Upon the implementation of a passively targeted drug delivery system, by virtue of the enhanced permeability and retention (EPR) effect, the accumulation of the active agent in tumours and in tumour cells can be increased substantially.



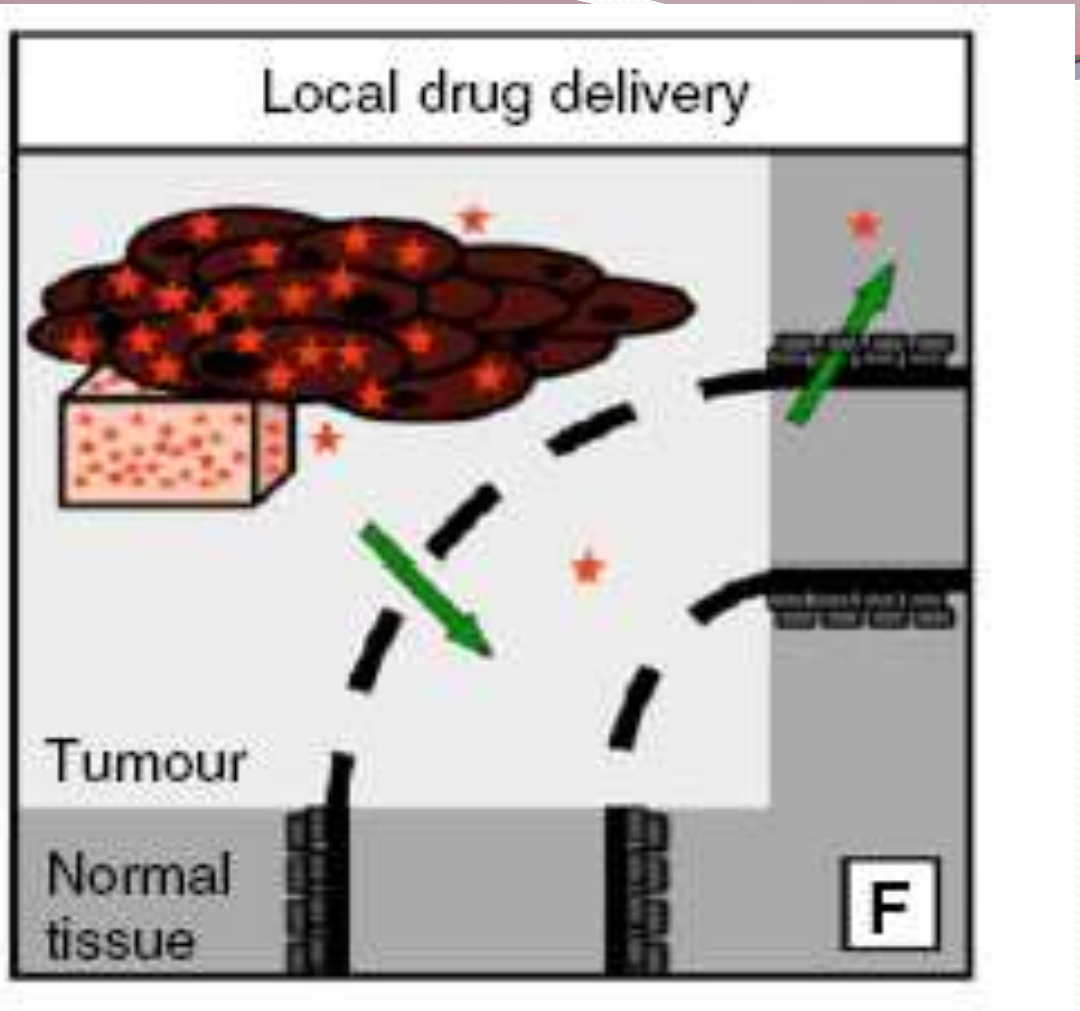
✓Active drug targeting to internalization-prone cell surface receptors (over)expressed by cancer cells generally intends to improve the cellular uptake of the nanomedicine systems, and can be particularly useful for the intracellular delivery of macromolecular drugs, such as DNA, siRNA and proteins.



✓Active drug targeting to receptors (over)expressed by angiogenic endothelial cells aims to reduce blood supply to tumours, thereby depriving tumour cells from oxygen and nutrients.



✓Stimuli-sensitive nanomedicines, such as Thermodox, can be activated (i.e., induced to release their contents) by externally applied physical triggers, such as hyperthermia, ultrasound, magnetic fields and light.



✓In cases in which tumours are easily accessible, for example during surgery, sustained-release delivery devices can be implanted or injected directly into (the irresectable parts of the) tumours.