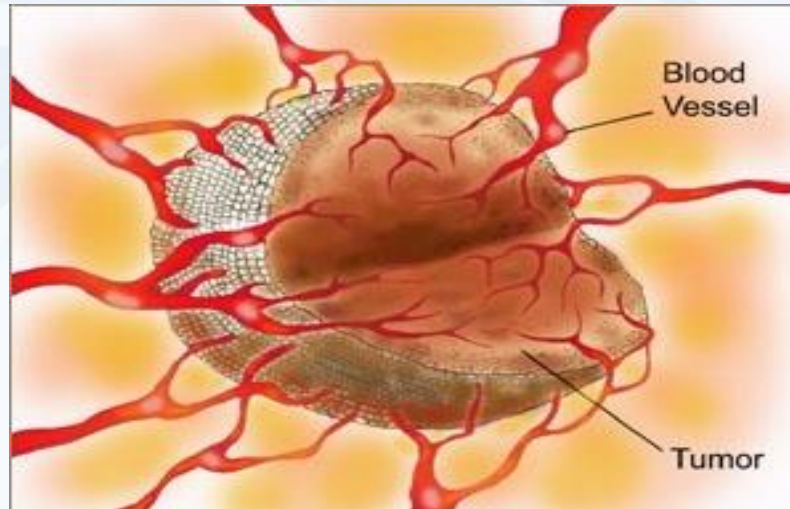


A Lecture on Tumor Targeted Drug Delivery System



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- Cancer is a disease in which cell division is **uncontrolled** and spread within the body of abnormal form from body's own cells.
- Tumor may be fluid filled or solid
- **Types** - Benign tumor(Non-cancerous)
 - Malignant tumor(Cancerous)
- **Traditional chemotherapy** – serious side effects



Differences



Normal tissue

- Normal vasculature
- Lymphatic drainage developed
- Normal pH

Tumor tissue

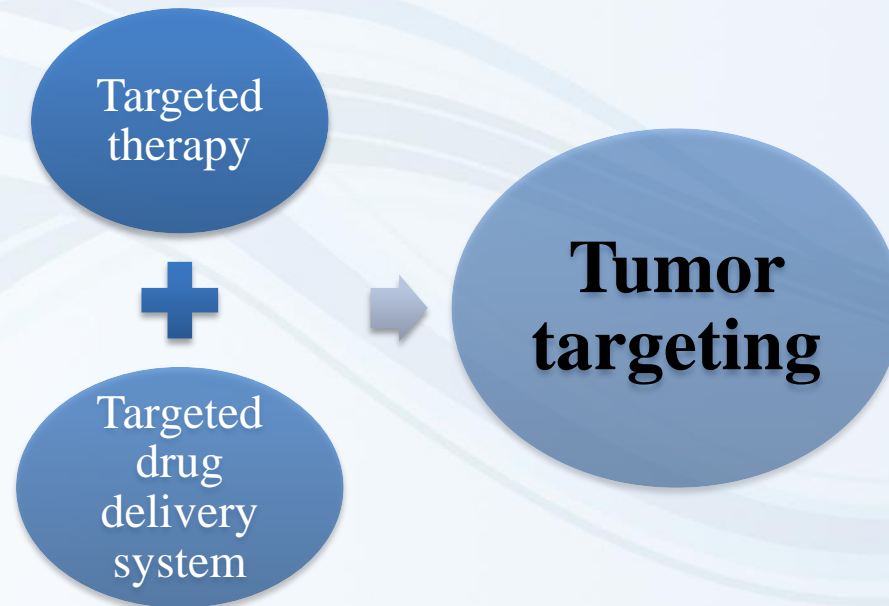
- Leaky vasculature
- Impaired lymphatic drainage
- Low intracellular pH

A blue notepad with rounded corners is shown at an angle. A blue pencil with a silver eraser and a sharpened orange tip is tucked into the top-left corner. The words "TUMOR TARGETING" are written in white, bold, uppercase letters across the center of the notepad. The background is a light blue gradient with faint, curved lines.

TUMOR TARGETING

Tumor targeting: Specific interaction between drug and its receptor at the molecular level.

- A rapidly growing tumor requires various nutrients and vitamins. Therefore, tumor cells over express many tumor-specific receptors which can be used as targets to deliver cytotoxic agents into tumors.



Targeted therapy

- It is a type of medication that blocks the growth of cancer cells by interfering with specific targets which are needed for carcinogenesis and tumor growth

Targeted drug delivery

- Refers to predominant drug accumulation within a target zone that is independent of the method and route of drug administration

Targeted drug delivery

- Targeted drug delivery system is achieved with the advantage of **morphology and physiological differences** between the normal cells and tumor cells.
- An **ideal anticancer drug delivery system** should fulfill the following requirements
 - Effectively kill tumor cells
 - Be non-toxic for healthy organs, tissues, and cells
 - Not induce multidrug resistance

Drug targeting to tumor is based on

- EPR effect(Enhanced Permeability and Retention)
- Nanoparticle properties and design
- Ligand-receptor interactions



Molecular targets for Tumor therapy

Altered expression of cell adhesion molecules

Altered expression of receptors during certain stages of cellular differentiation, like transferrin receptors, folate receptors, etc.

Altered expression of certain growth factors like epidermal growth factor receptor (EGFr).

Expression of tumor vasculature epitopes.

Expression of surface determinants on malignant cells, like tumor associated genes(TAA).



PRINCIPLES OF TUMOR TARGETING

Principles of drug targeting to tumors

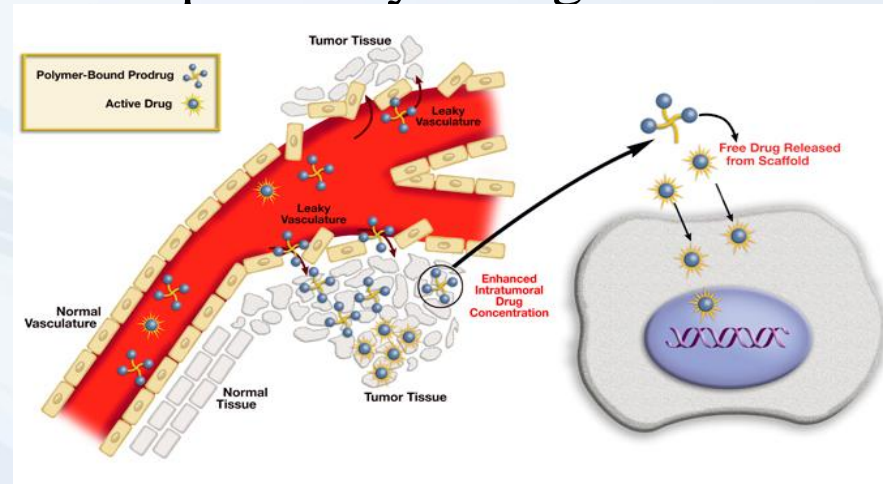
- Passive targeting,
 - Active targeting to cancer cells
 - Active targeting to endothelial cells
 - Triggered drug delivery (using stimuli-responsive carrier materials).
-
- Site specific drug delivery requires localization of drug and carrier within the desired target organ.
 - The role of carrier systems in providing site specificity can be evident from the terms **passive and active targeting** approaches

Passive targeting

- Passive targeting involves therapeutic exploitation of the natural distribution pattern of a drug-carrier construct in vivo.
- For e.g., the role of RES in clearing foreign particulate materials from blood permits drug encapsulated in particulate carriers like liposomes to be passively targeted to macrophages.

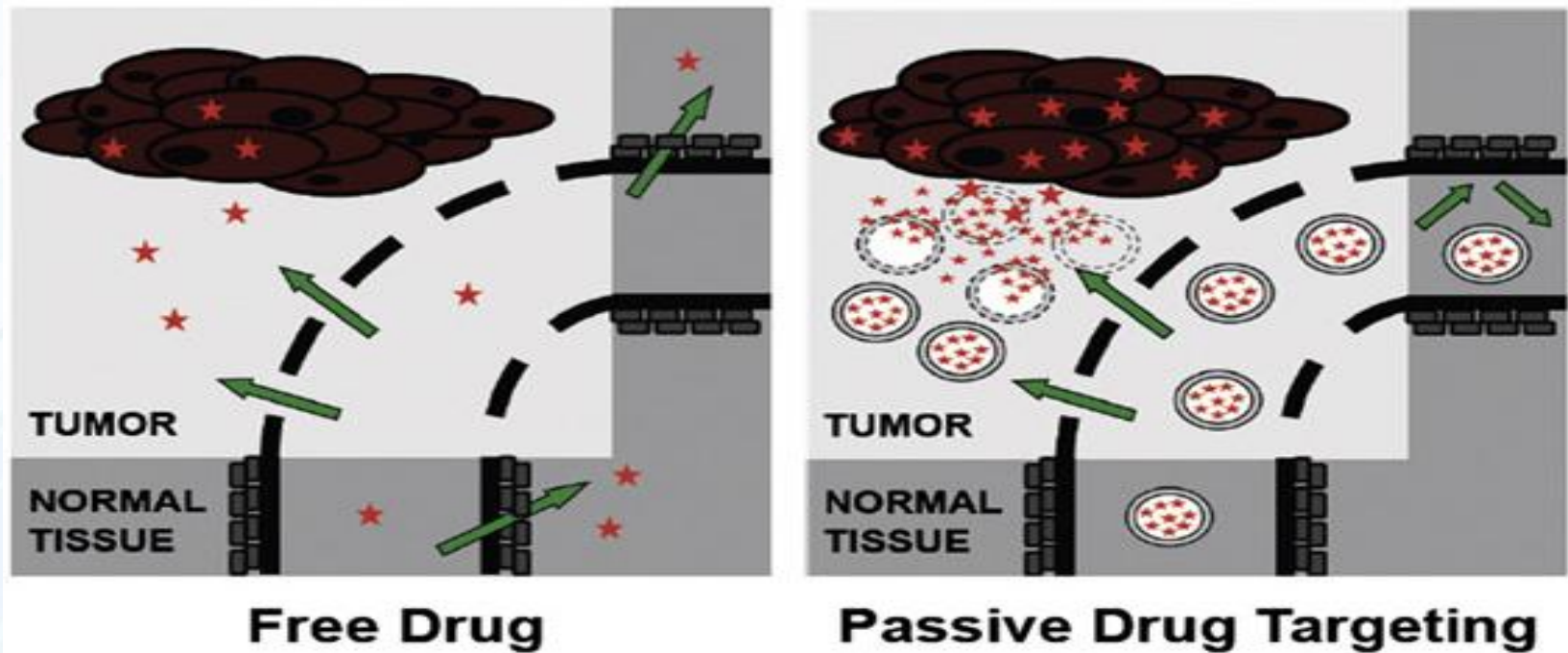
- Passive targeting is based on drug accumulation in the areas around the tumors with leaky vasculature; commonly referred

to **Enhanced Permeation and Retention (EPR) effect**



Enhanced Permeability and Retention effect(EPR)

- Leaky vasculature
- Impaired lymphatic drainage
- Renal clearance
- Reticuloendothelial System uptake(RES)



Classification of Tumor targeted drug delivery systems

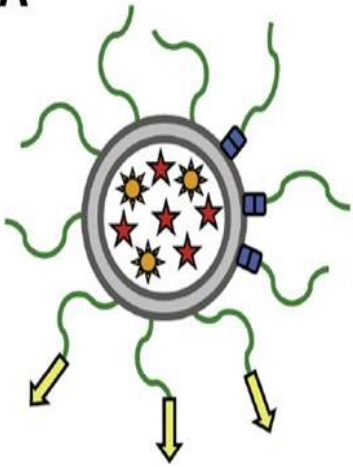
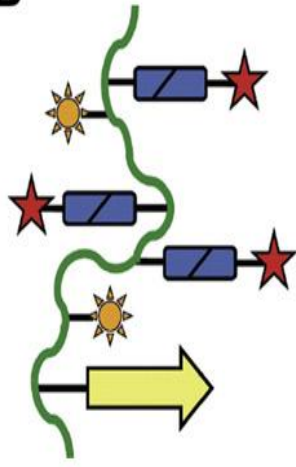
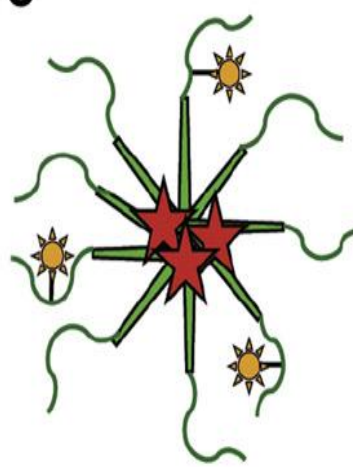
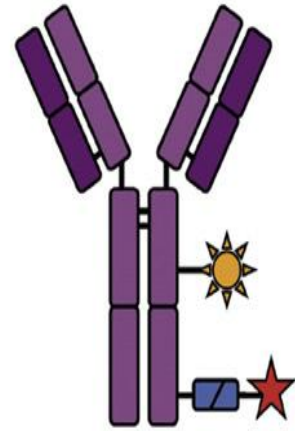
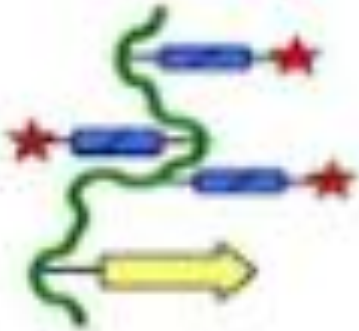
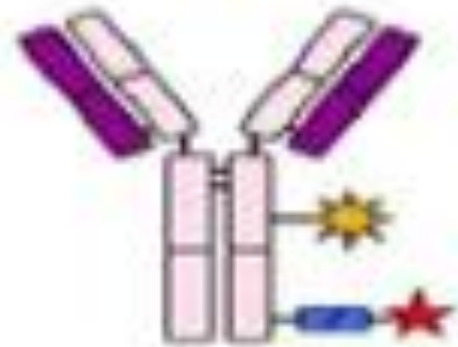
Tumor targeted drug delivery system

Macromolecular conjugates

- Polymer-drug conjugate
- Protein-drug conjugate
- Antibody-drug conjugate

Particulate systems

- Liposomes
- PEGylated liposomes
- Polymeric micelles

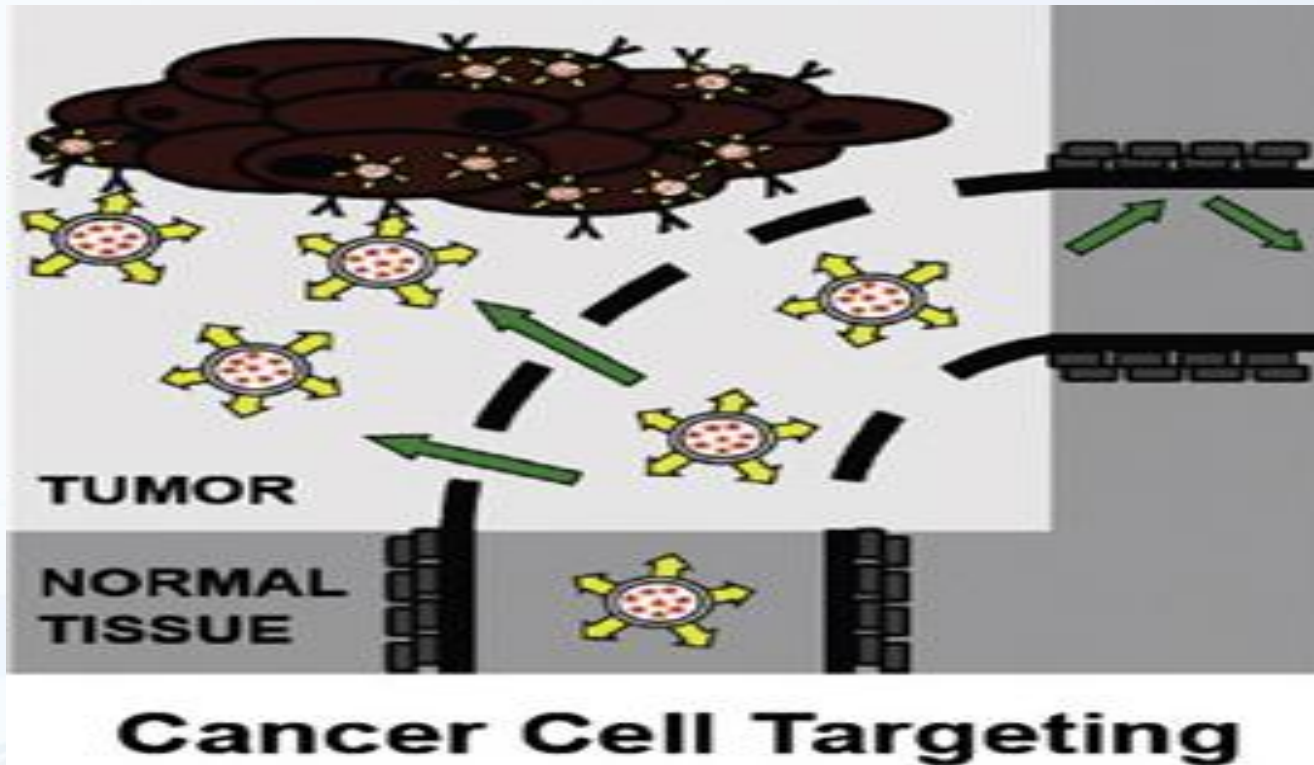
A**Liposome****B****Polymer****C****Micelle****D****Nanoparticle****E****Antibody****Polymer–drug conjugate****Protein–drug conjugate****Antibody–drug conjugate**

Approved passive Tumor targeted drug delivery systems

Nanocarriers	Drug	Name	Indications
Nanoparticles	Doxorubicin	Transdrug [®]	Hepatocarcinoma
Liposomes	Doxorubicin	Myocel [®]	Breast cancer
(PEGylated)	Doxorubicin	Doxil [®]	Ovarian cancer

Active targeting to cancer cells

- “Active targeting” is used to describe specific interactions between drug/drug carrier and the target cells, usually through specific ligand–receptor interactions
- The term “active targeting” simply means a **specific ligand–receptor type interaction** for intracellular localization which occurs only after blood circulation and extravasation
- Active drug targeting is generally implemented to improve **target cell recognition and target cell uptake**, and not to improve overall tumor accumulation.
- Ligand mediated targeting is the major focus of the current research that involves ligands developed against cell receptors or antigenic determinants expressed on tumor cells or vasculature.



Examples of targeting ligands used for active targeting

- Folate
- Transferin
- Galactosamine

Elements of active targeted drug delivery system



Active targeting moieties

- Monoclonal antibodies recognize the protein(antigen) on the surface of the cancer cell and lock onto it.

Some of the most exploited targets for antibody targetin are:

- Transferrin receptors – High level of transferrin receptors on glioma cells
- Fibronectin – Expressed in and around neoplastic blood vessels during angiogenesis
- Epidermal growth factor receptor – Over expressed in a portion of breast cancers and other solid tumors
- Vascular endothelial growth factor – Expressed in neoplastic blood vessels

E.g., Antibody---Mylotarg---CD33-targeted ozogamycin
gemtuzumab---Leukemia.

Immunoconjugates

Combine the targeting power of mABs and cytotoxic activity of drugs

- Radio active substances
- ADEPT
- Drugs or toxins

Vitamins as Active targeting moieties

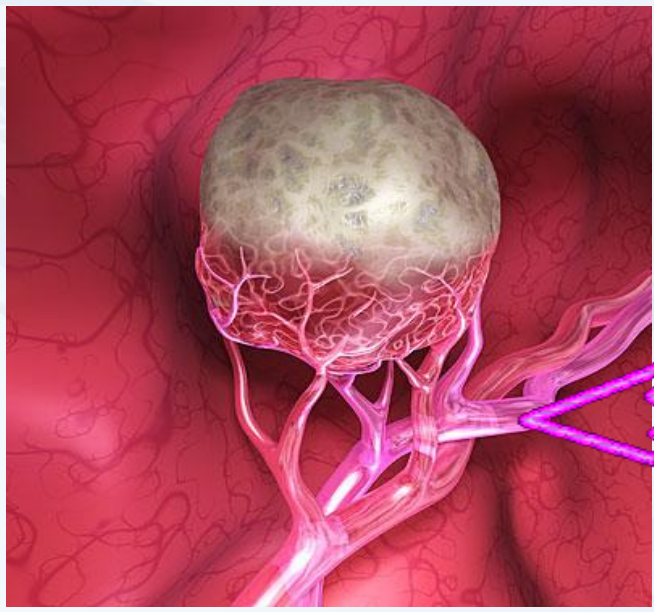
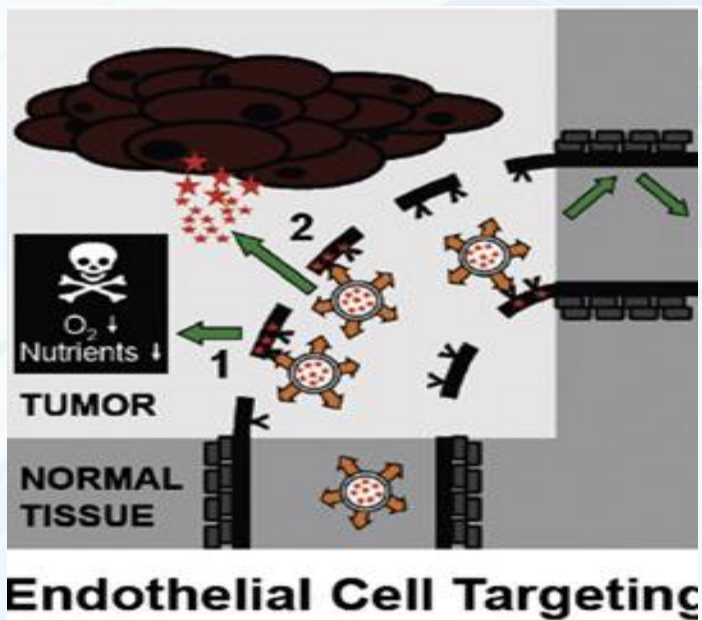
- The folate receptor is significantly upregulated on many cancer cells compared to normal tissue
- Normal cells transport a reduced folate across their membranes but will not transport folate conjugates of any type
- Malignant cells transport folate conjugates through the folate receptor, which is considered the alternative route

Active targeting to vasculature

- Tumor vasculature-targeted nanomedicines do not depend on extravasation and penetration across pericyte-, smooth muscle cell- and/or fibroblast-based cell layers.
- As they encounter their target receptors much more frequently and since they do not suffer from the high tumor cell density and the high interstitial fluid pressure that unfavorably affect cancer cell-targeted nanomedicines
- Thus endothelial cell-targeted nanomedicines possess significantly more potential for improving antitumor efficacy

These not only bind and kill endothelial cells but also

- Thereby depriving tumors of oxygen and nutrients
- They can be designed to release their contents within the tumor vasculature upon binding to tumor blood vessels, thereby enabling low-molecular-weight drugs to penetrate deep into the tumor interstitium



Tumor vasculature targeting

Advantages of Tumor Vasculature Targeting over Tumor Cell Targeting

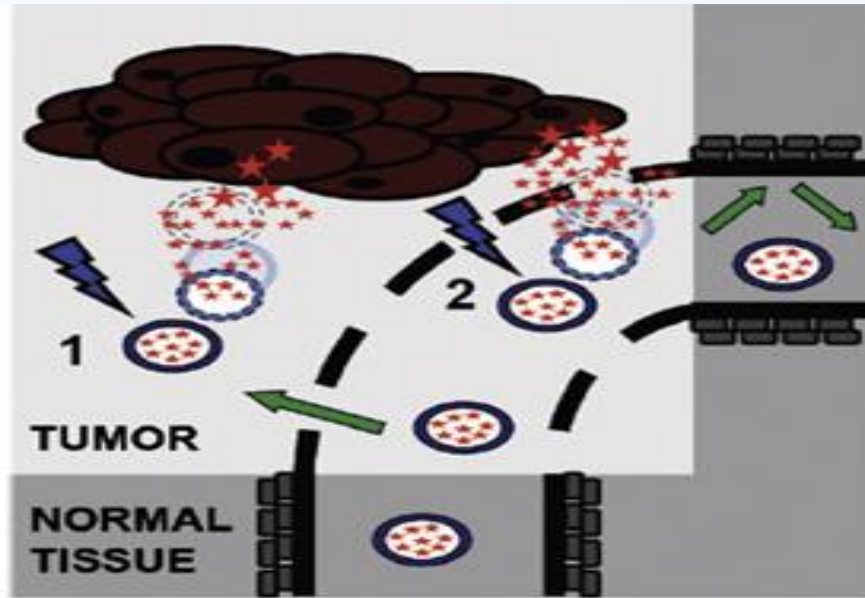
- Easy access to target cells upon i.v. injection
- Independent of the type of solid tumor
- Active on metastases
- Overcomes acquired and intrinsic drug resistance

Vasculature targeted drug delivery system

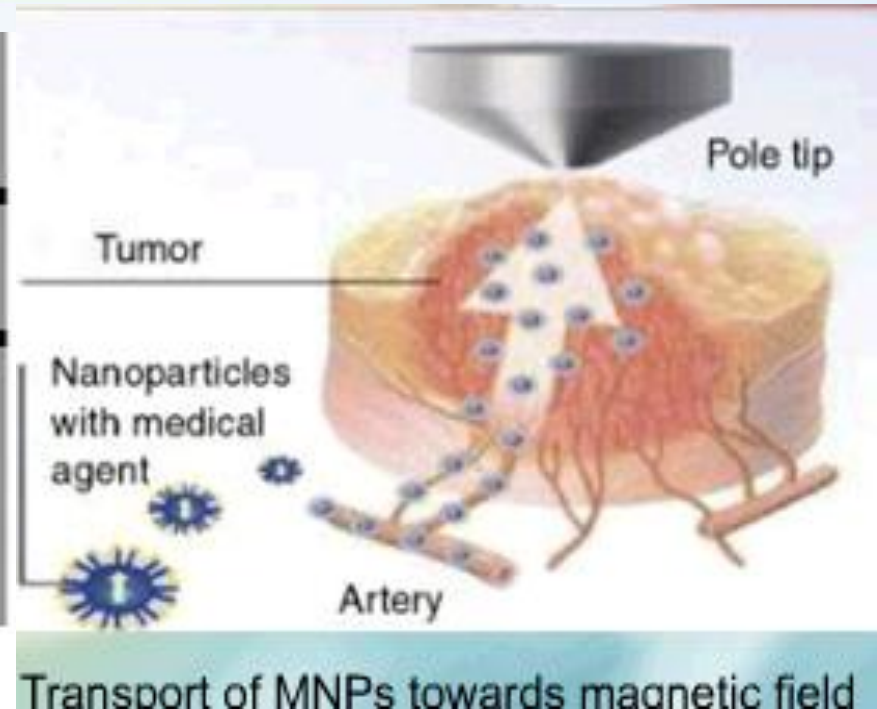
TVT-Dox = NGR-targeted Liposomal Dox

Triggered drug delivery

- The tumor microenvironment differs from that normal cells microenvironment
- Advantage of the difference in pH, temperature is used to release the drug in the tumor microenvironment
- It employs drug-carrier constructs that release drug only when exposed to specific microenvironments such as change in pH and temperature .
- The drug release also triggered on subjecting to the external magnetic fields
- Thermosensitive liposomes – Destabilisation of lipid membranes at mild hyperthermia



Triggered Drug Release

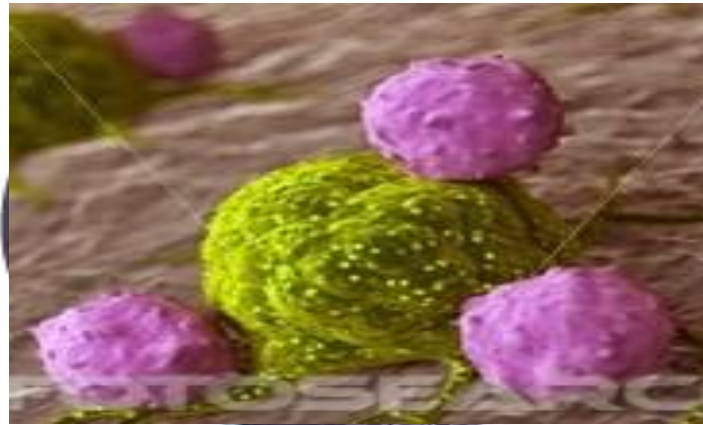


Transport of MNPs towards magnetic field

Simuli-responsive nanomedicines

- Thermodox (i.e. temperature-sensitive PEGylated liposomes containing doxorubicin)
- Tamoxifen-loaded Fe_3O_4 /poly(L-lactic acid) nanoparticles --- Breast cancer

Marketed Products



Conclusion

- Tumor targeting can be achieved through passive and active targeting approaches
- Several systems have been demonstrated excellent tumor targeting properties such as macromolecular conjugates, liposomes, polymeric micelles.
- Anticancer drugs with different physiochemical properties are delivered by these drug delivery systems and a number of targeting ligands were successfully incorporated to enhance tumor specific targeting
- An optimal tumor targeted delivery system shall be realized in the near future

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REFERENCES



REFERENCES

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