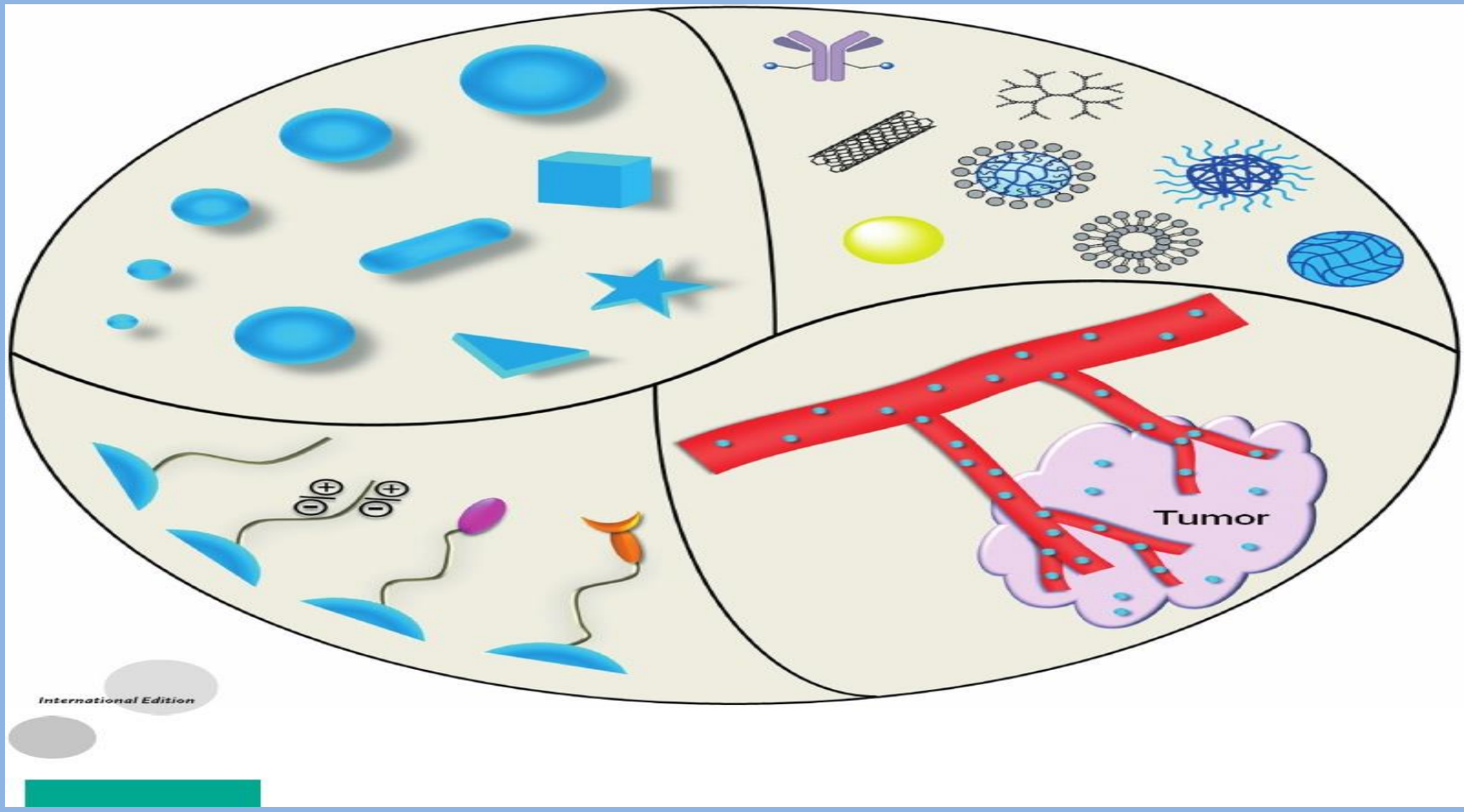


Dr M.Amer Al chikh youssef

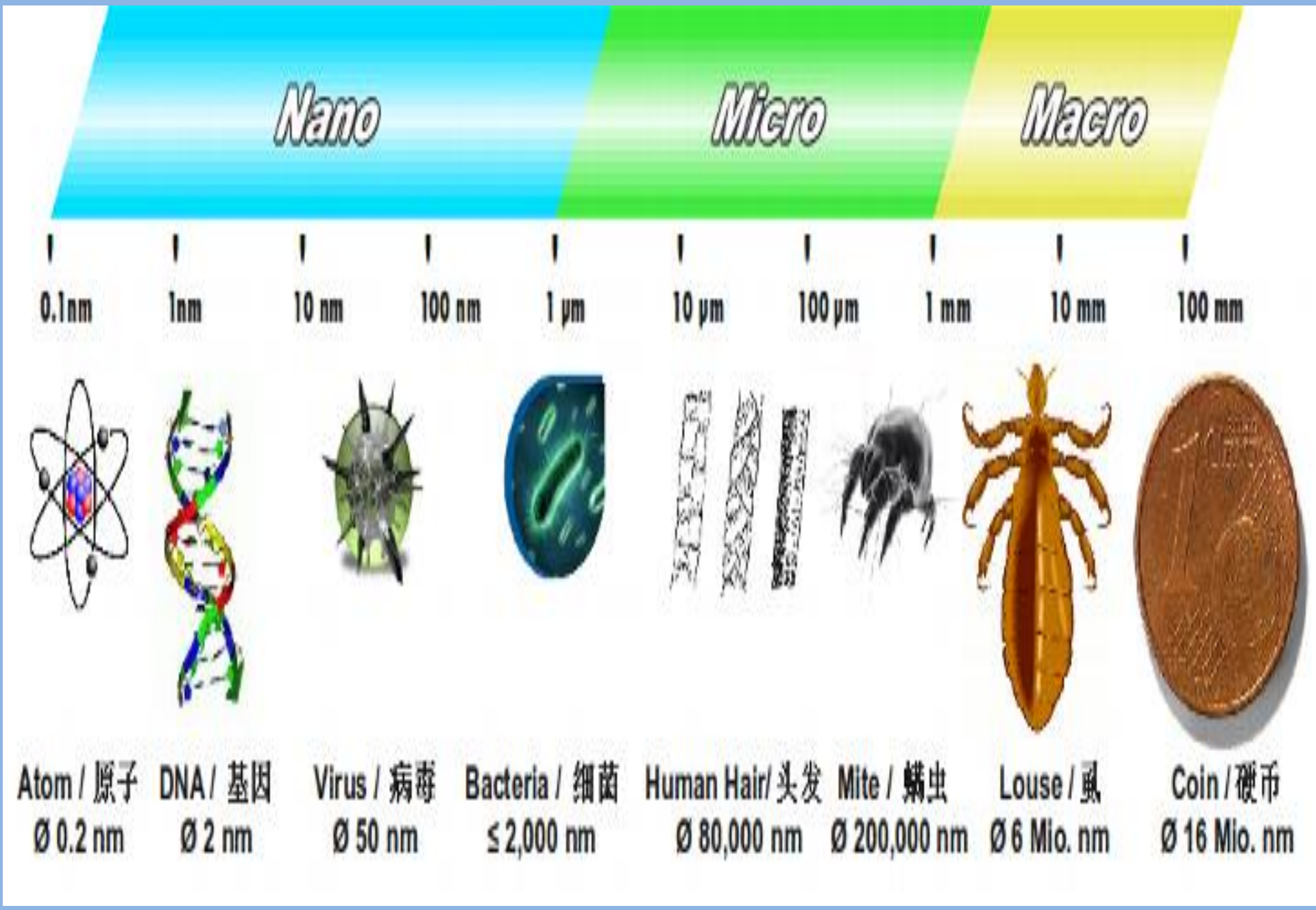
What is Nanotechnology?

- **Basic Definition:** Technology of building or creating products such as electronic circuits from single atoms and molecules
  - Deals with the making of materials by molecular self assembly
  - Rearranging atoms to get:

- **Manufactured products:**
  → made from atoms

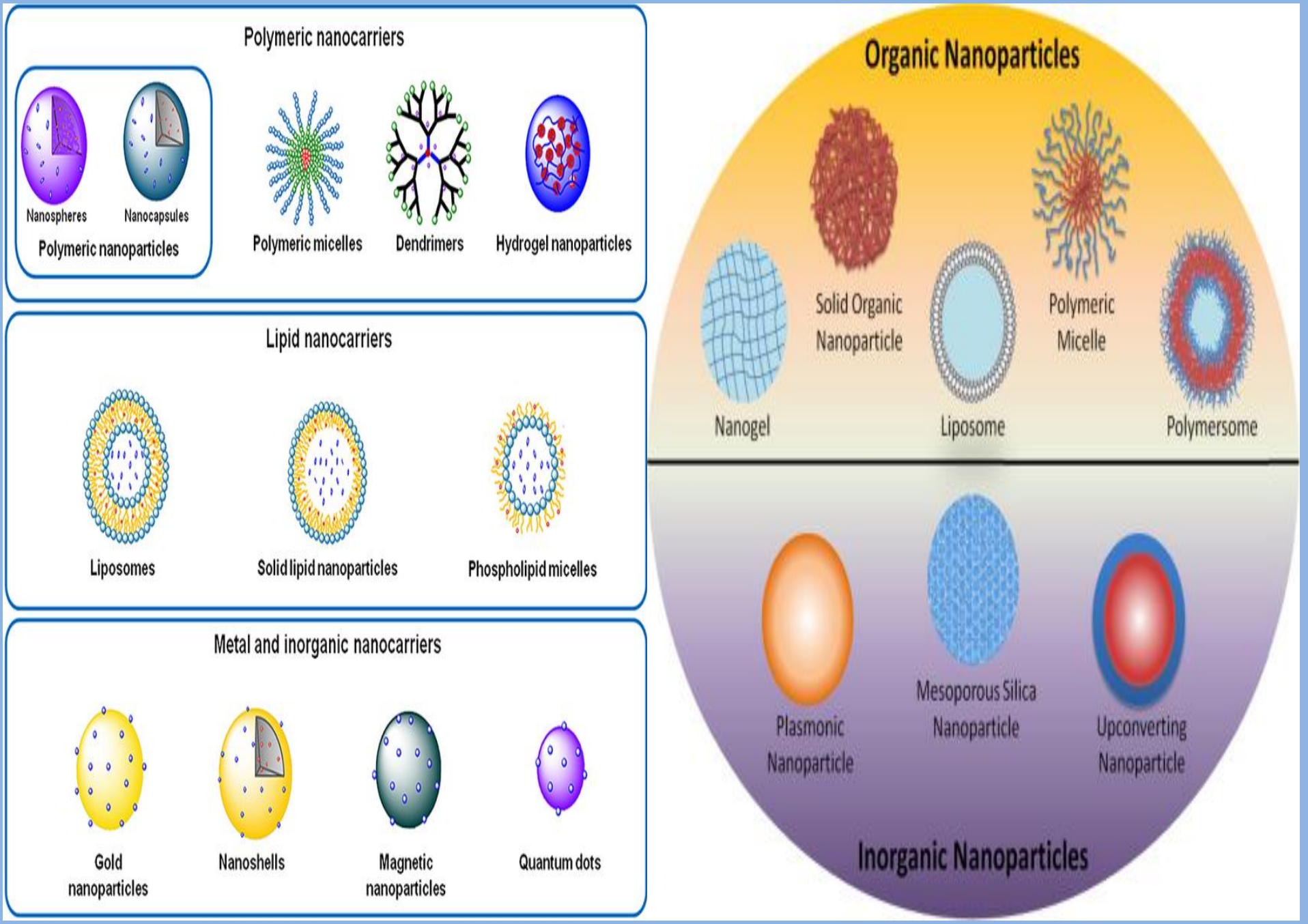
- **Properties of products:**
  → depends on how atoms are arranged

For instance, if we rearrange the atoms of coal, we can make diamond if we rearrange the atoms in dirt water or air, we can end up with potatoes!


Nano
Micro
Macro
0.1nm
1nm
10 nm
100 nm
1 µm
10 µm
100 µm
1 mm
10 mm
100 mm
Atom / 原子
Ø 0.2 nm
DNA / 基因
Ø 2 nm
Virus / 病毒
Ø 50 nm
Bacteria / 细菌
≤ 2,000 nm
Human Hair/ 头发
Ø 80,000 nm
Mite / 螨虫
Ø 200,000 nm
Louse / 虱
Ø 6 Mio. nm
Coin / 硬币
Ø 16 Mio. nm

A Brief History of Nanotechnology

- On **December 29, 1959, physicist Richard Feynman gave a radical lecture** at an American Physical Society meeting at Caltech titled ***"There's Plenty of Room at the Bottom"*.**
- Feynman suggested that it should be possible to **make machines at a nano-scale that "arrange the atoms the way we want", and do chemical synthesis by mechanical manipulation.**
- This lecture was the **birth of the idea and study of nanotechnology.**


Polymeric nanocarriers
Nanospheres
Nanocapsules
Polymeric nanoparticles
Polymeric micelles
Dendrimers
Hydrogel nanoparticles
Lipid nanocarriers
Liposomes
Solid lipid nanoparticles
Phospholipid micelles
Metal and inorganic nanocarriers
Gold nanoparticles
Nanoshells
Magnetic nanoparticles
Quantum dots
Organic Nanoparticles
Nanogel
Solid Organic Nanoparticle
Liposome
Polymeric Micelle
Polymersome
Plasmonic Nanoparticle
Mesoporous Silica Nanoparticle
Upconverting Nanoparticle
Inorganic Nanoparticles

Nanoparticles

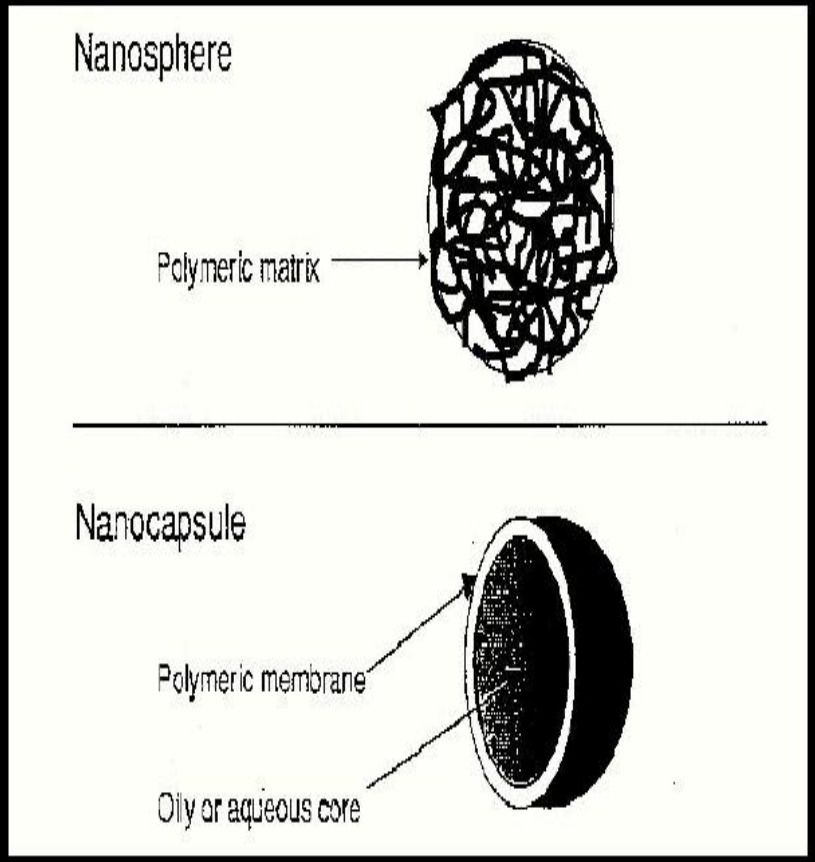
Nanospheres

Nanoencapsules

Matrix type structure in which a drug is dispersed

Membrane wall structure with an oil core containing drug

Nanospheres and Nanocapsules



- **Chemotherapy:**
  - Drugs that effect cells that are doubling
  - Not very specific
  - Mostly intravenous, some oral agents
  - Cytotoxic

Side Effects of Chemotherapy

a. Myelosuppression
- Neutropenia
- Anemia
- Thrombocytopenia

b. GI and Mucosal Side Effects
- Nausea and Vomiting
- Diarrhea
- Mucositis
- Anorexia
- Constipation
- Perirectal cellulitis

c. Alopecia

d. Fatigue

e. Cardiac toxicity

f. Pulmonary toxicity

g. Hemorrhagic cystitis

h. Hepatotoxicity

i. Nephrotoxicity

j. Neurotoxicity

k. Alterations in sexuality and reproductive function

l. Cutaneous Reactions
- Acral erythema
- Hyperpigmentation
- Inflammation of keratoses
- Nail changes
- Neutrophilic eccrine hydradenitis
- Radiation enhancement
- Radiation recall
- Hand-and-foot syndrome

m. Ocular Toxicity

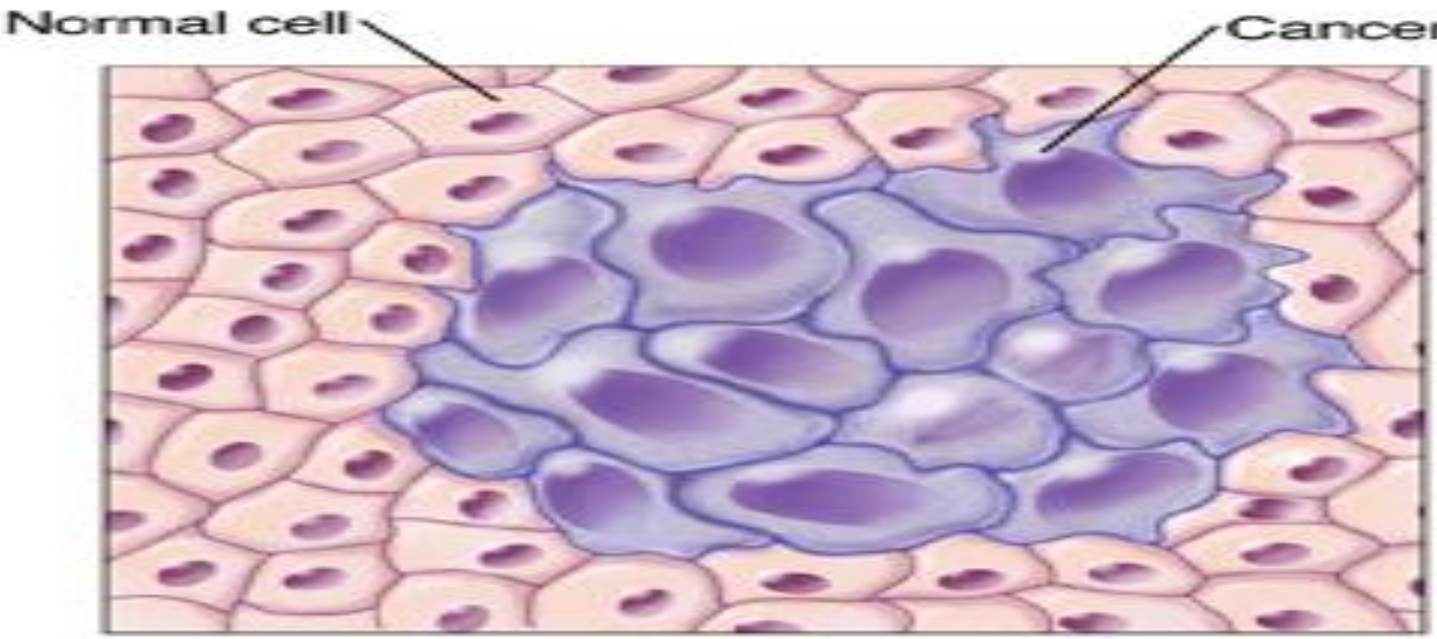
n. Secondary Malignancies

Conventional chemotherapy limitations

Washout form circulation (short time)

Poor solubility unable to penetrate biological membranes

MDR1 (P-Glycoprotein) prevent drug accumulation inside tumor

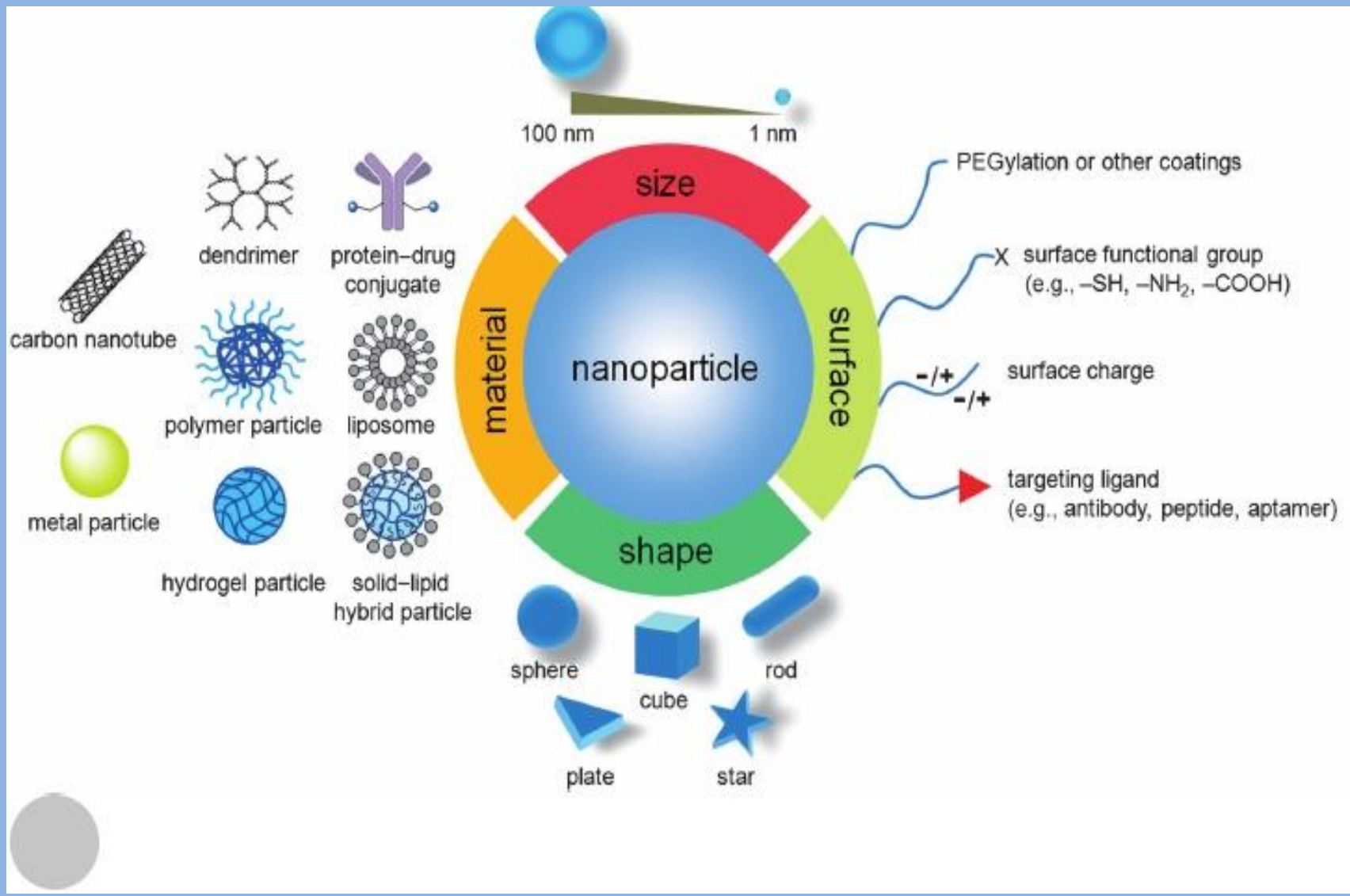


The main challenge of chemotherapy is to differentiate Cancerous cells and normal body cells

Chemotherapy fails to target cancer cells selectively

How can we improve therapeutic index of chemotherapy?

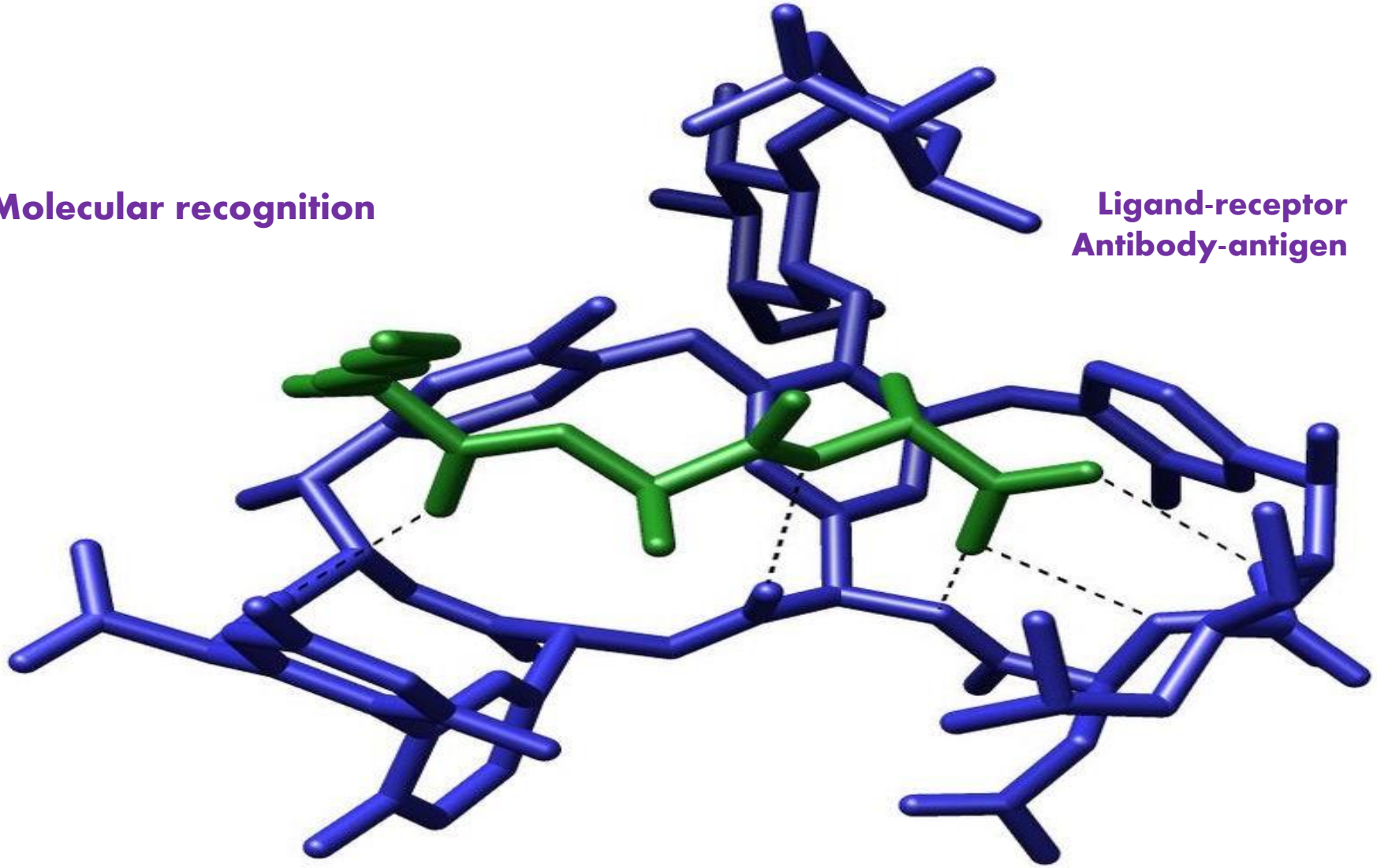
Nanotechnology is the grate revolution in targeting cancer cells



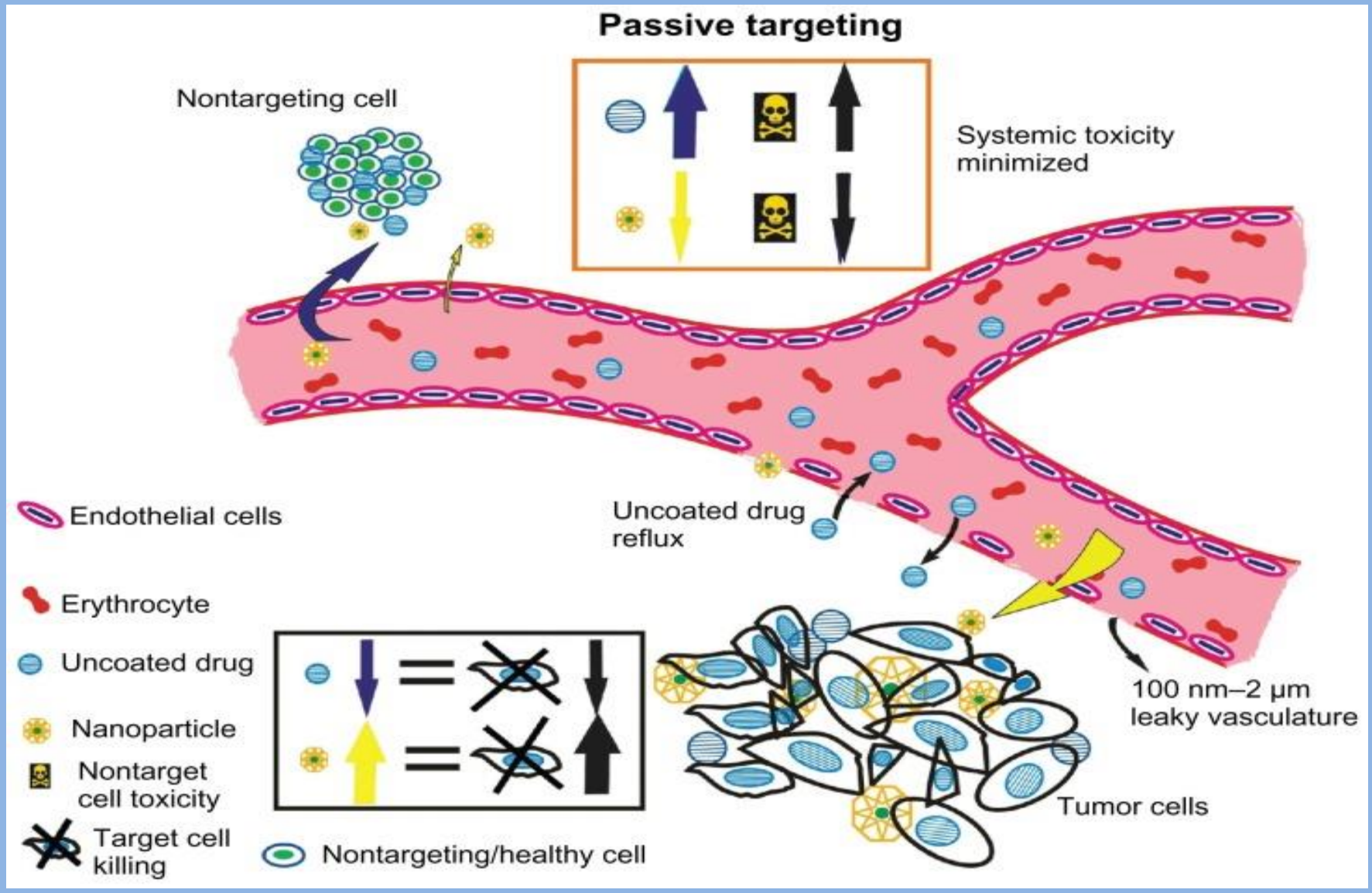
ACTIVE TARGETING

Molecular recognition

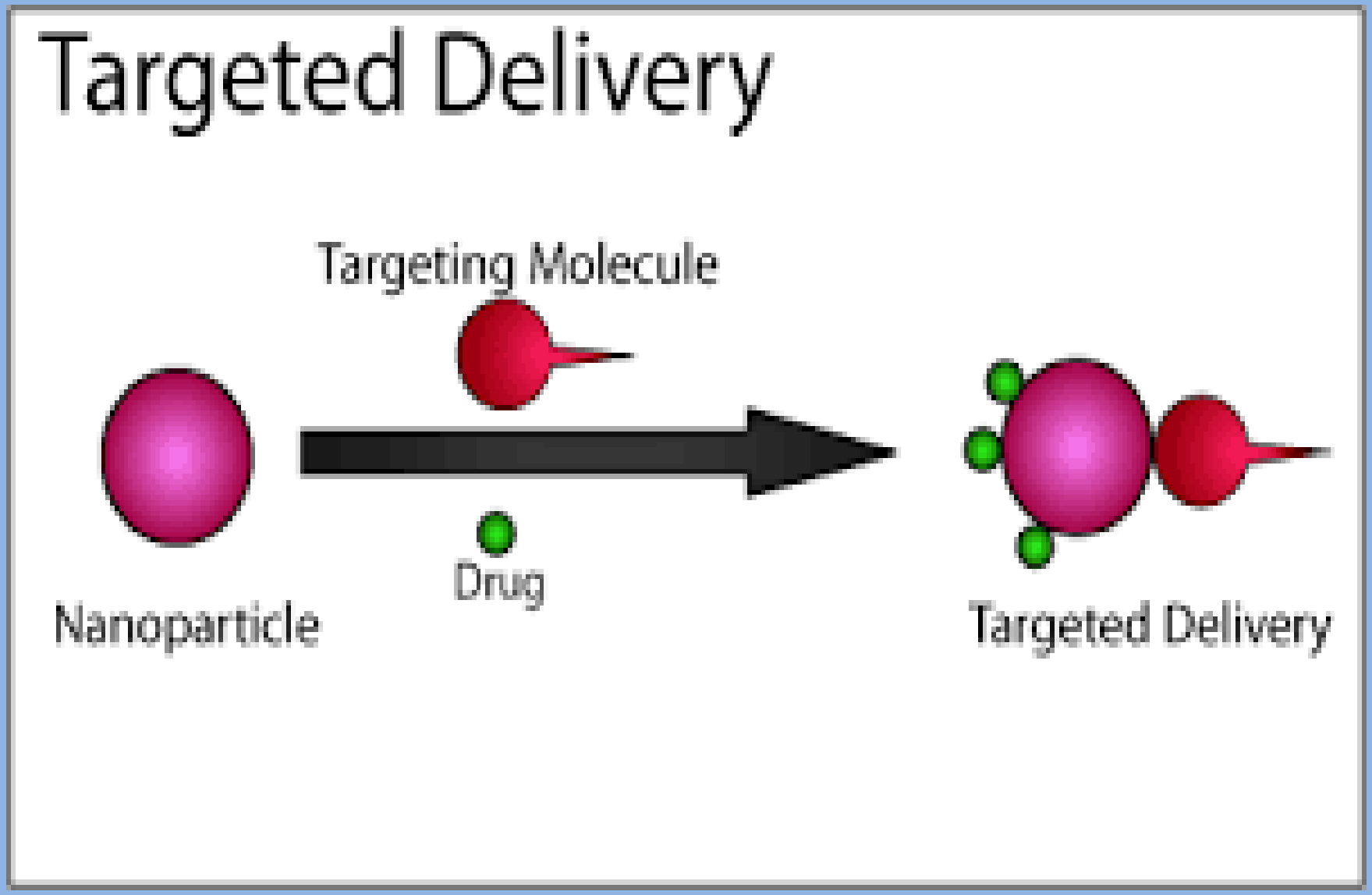
Ligand-receptor
Antibody-antigen



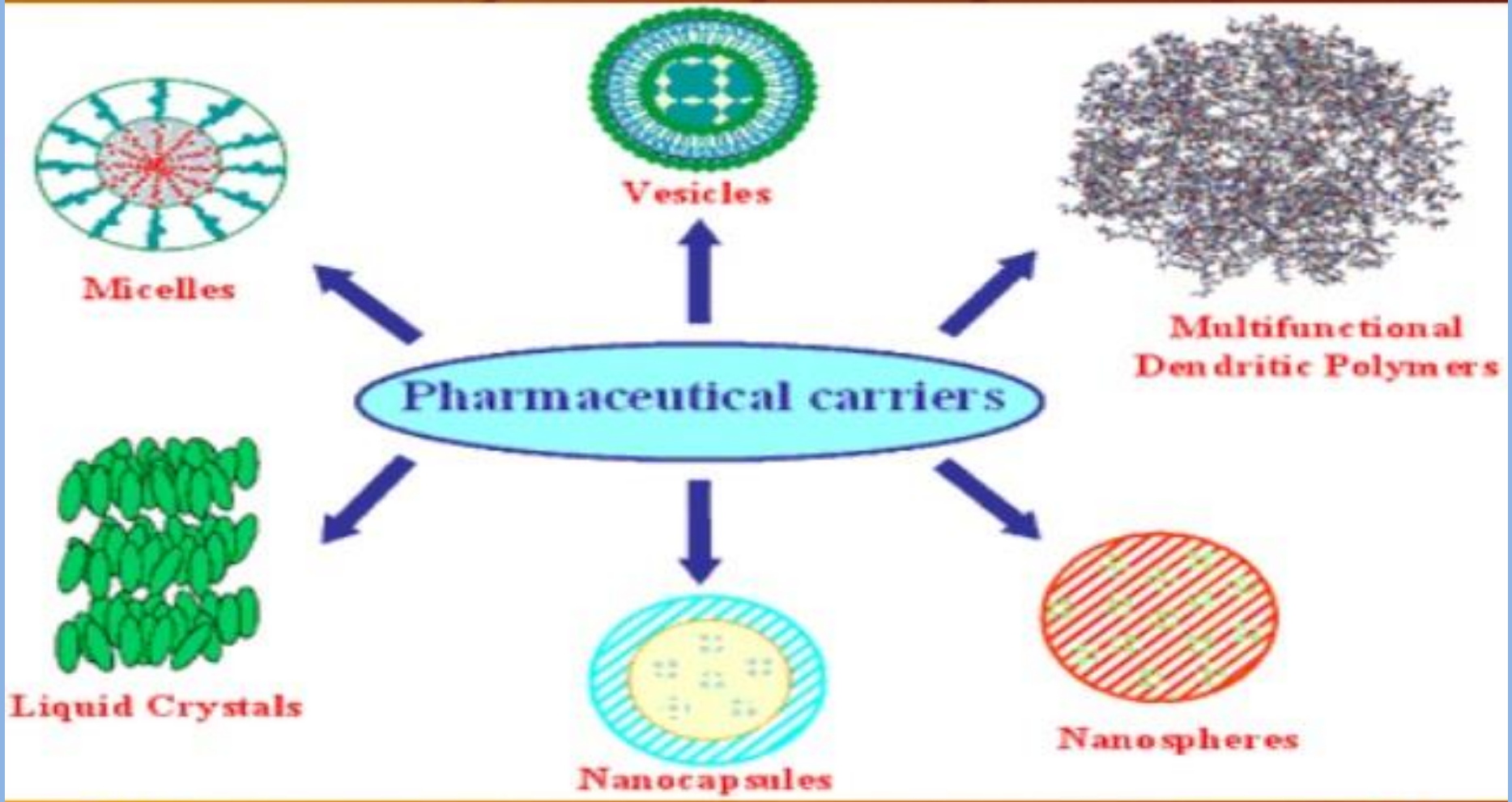
PASSIVE TARGETING



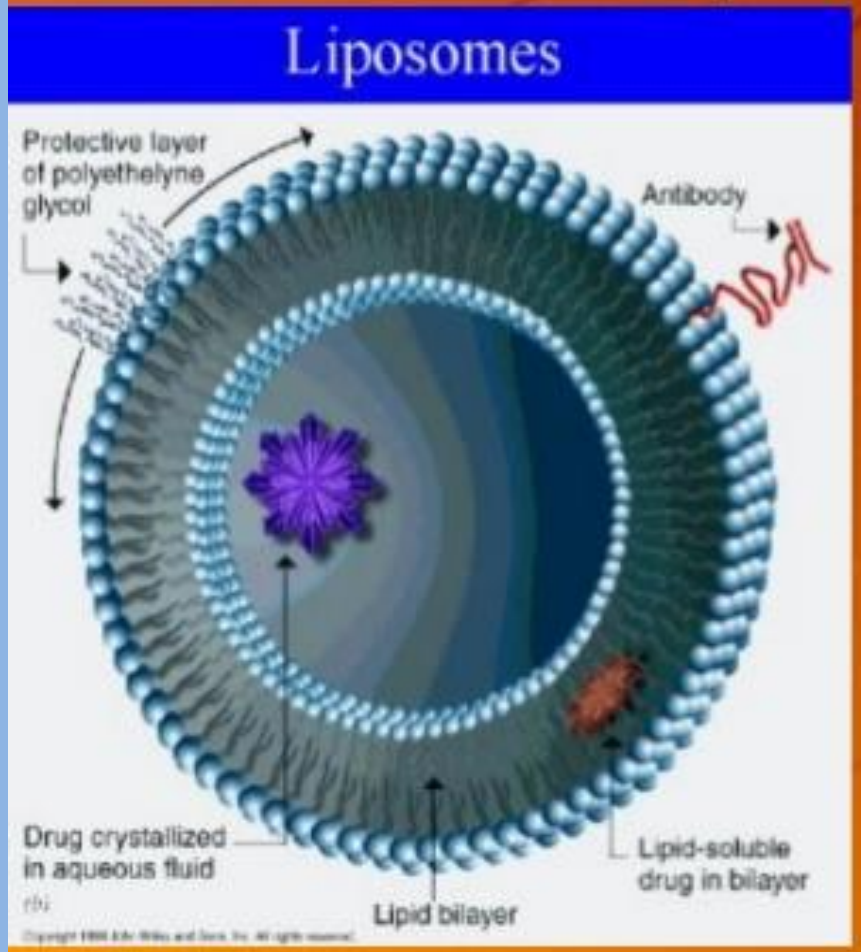
Nanotechnology targeted based delivery system

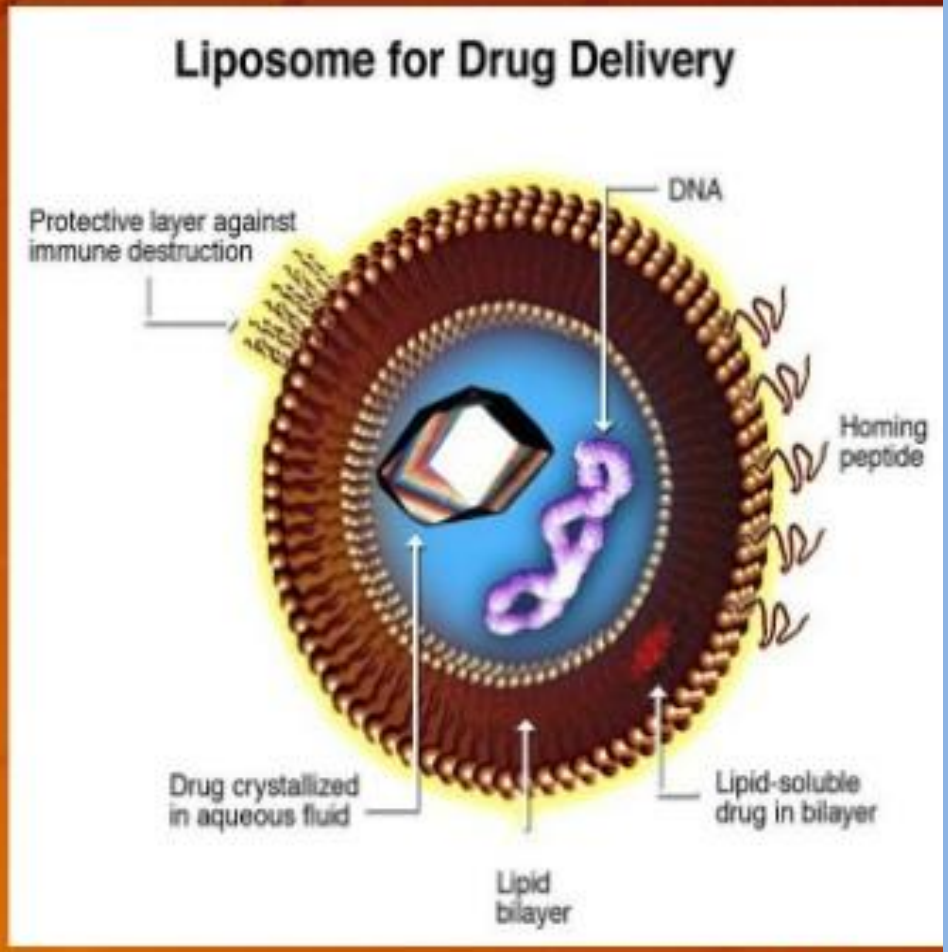


Drug Delivery Carriers

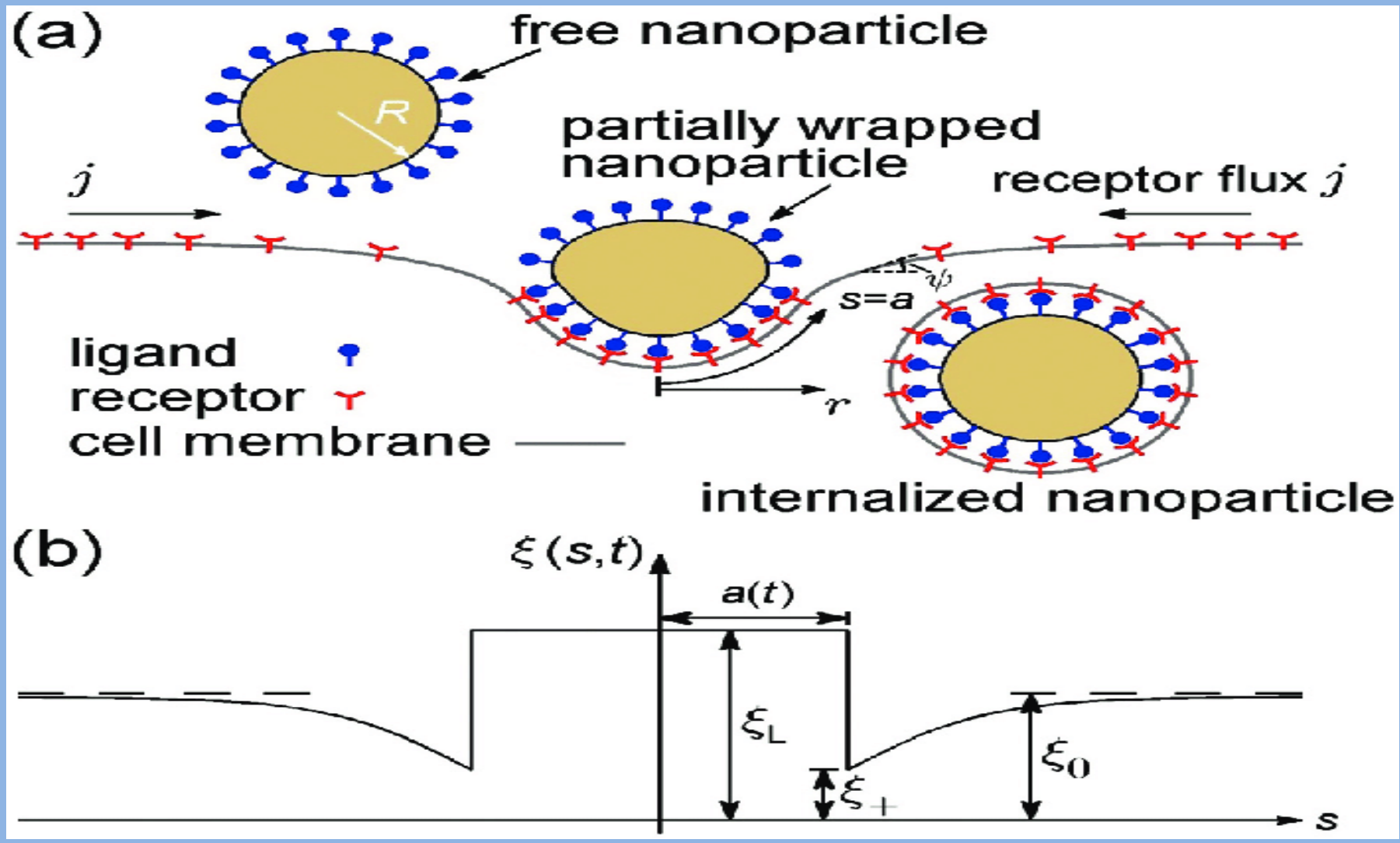


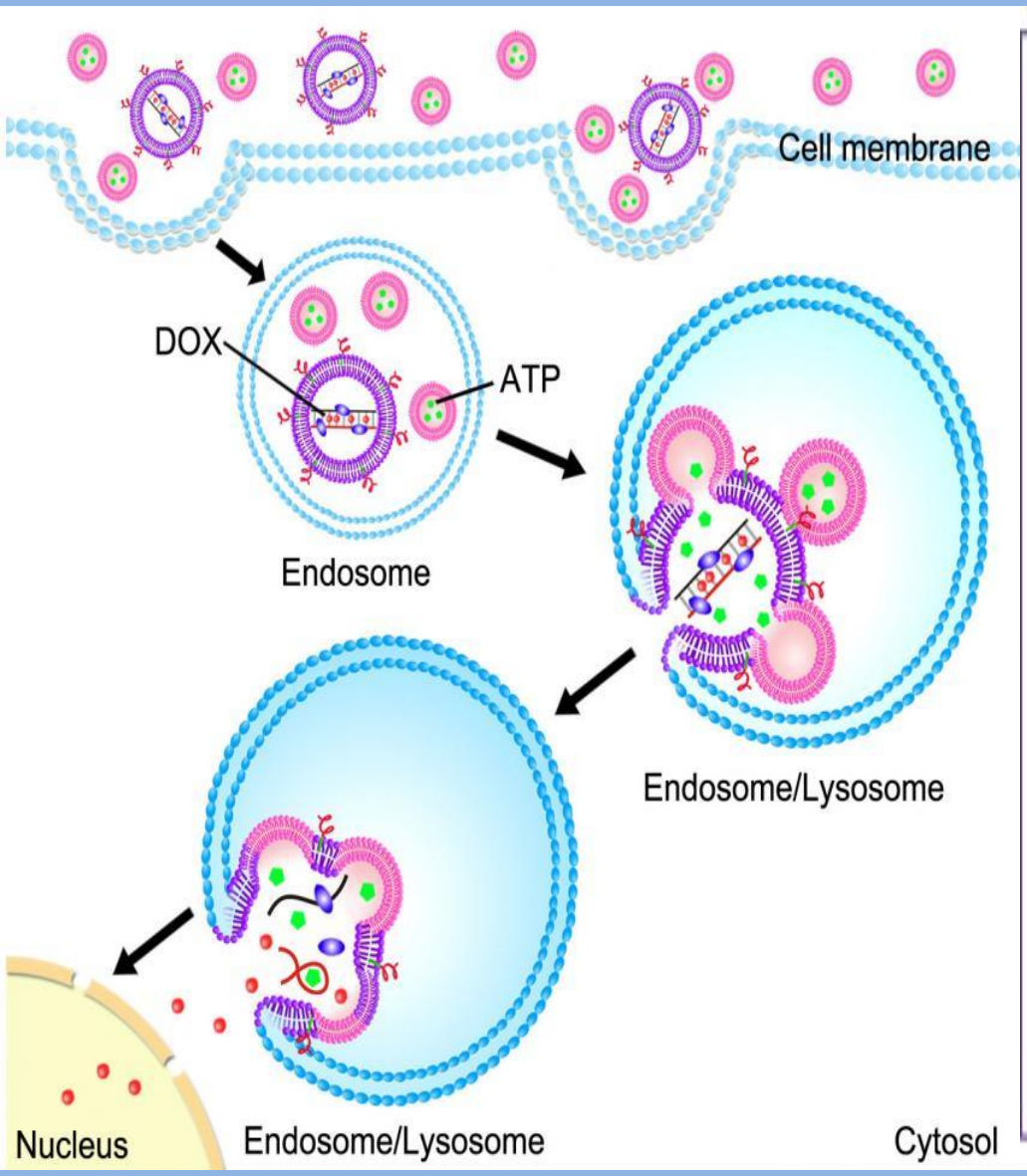
Liposome's

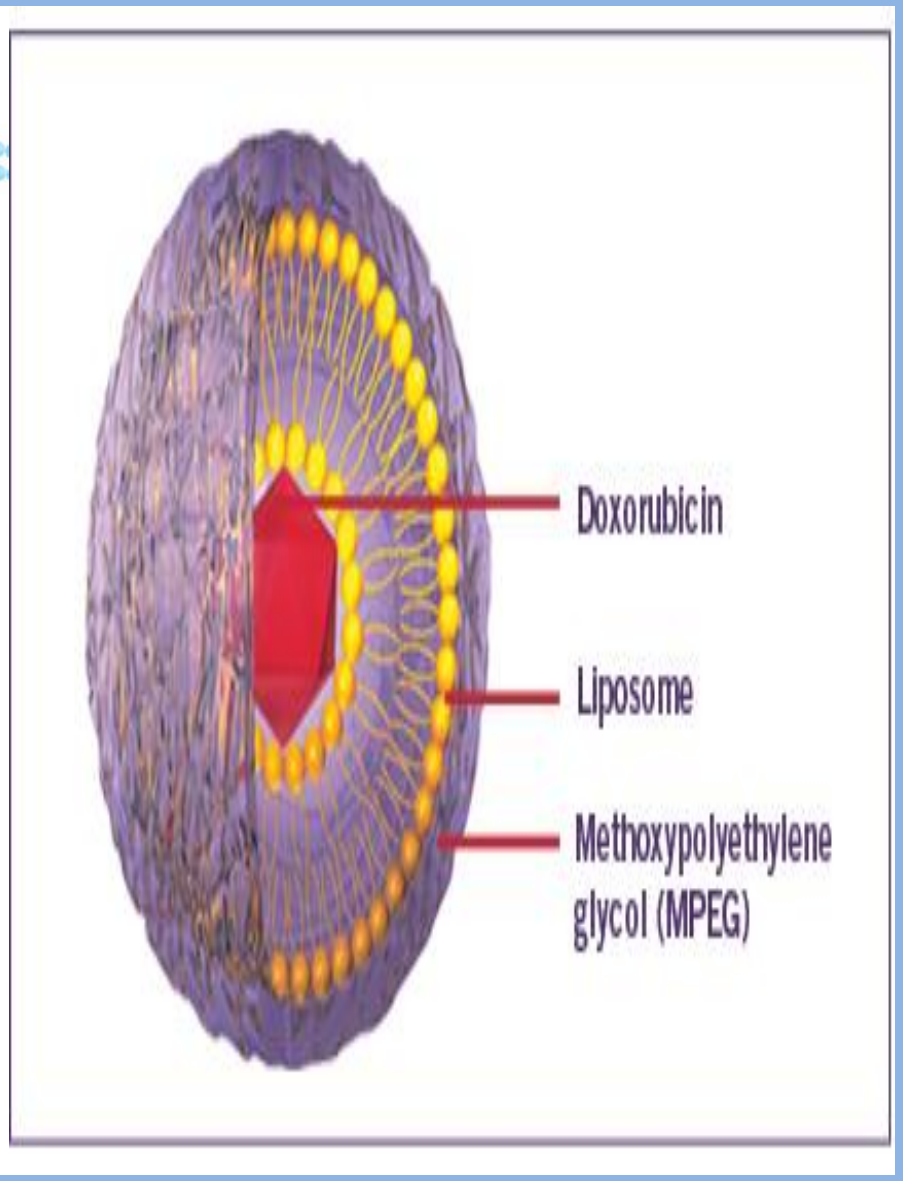

Liposomes
Protective layer of polyethelyne glycol
Antibody
Drug crystallized in aqueous fluid
Lipid bilayer
Lipid-soluble drug in bilayer


Liposome for Drug Delivery
Protective layer against immune destruction
DNA
Homing peptide
Drug crystallized in aqueous fluid
Lipid bilayer
Lipid-soluble drug in bilayer

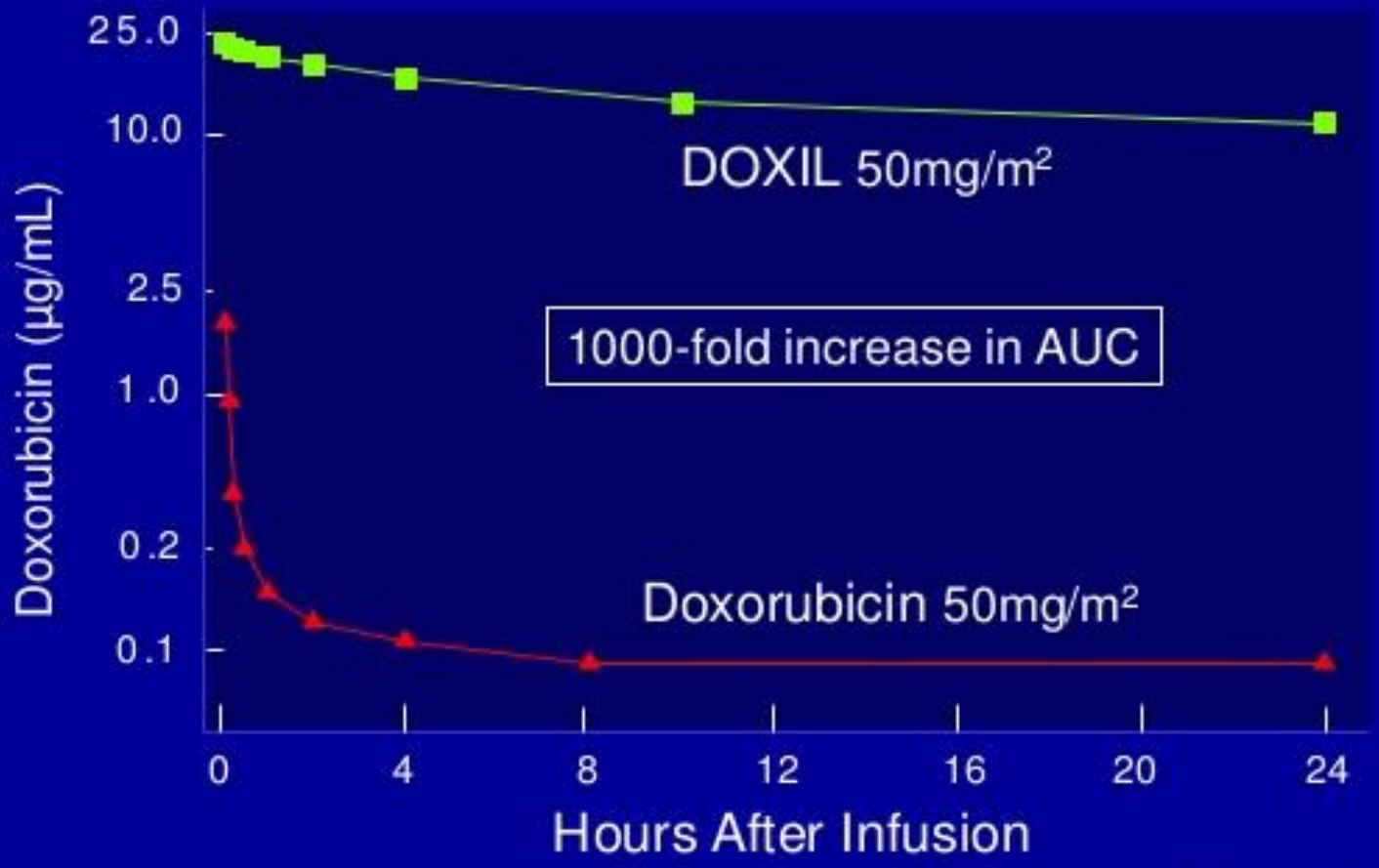
Receptor mediate endocytosis




Cell membrane
DOX
ATP
Endosome
Endosome/Lysosome
Nucleus
Endosome/Lysosome
Cytosol


Doxorubicin
Liposome
Methoxypolyethylene glycol (MPEG)

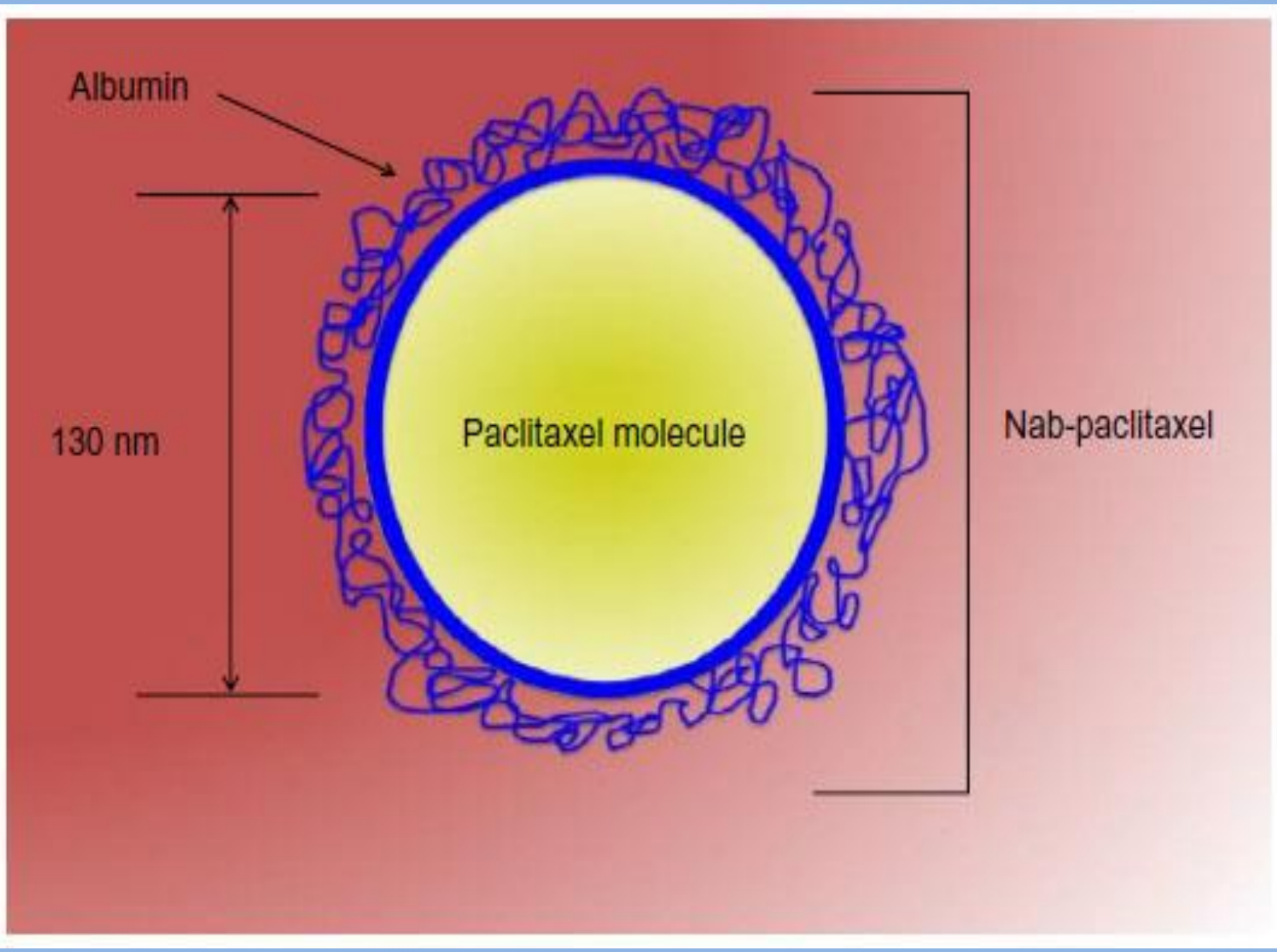
Plasma Levels in Humans: DOXIL vs. doxorubicin - Impressive change in PK profile

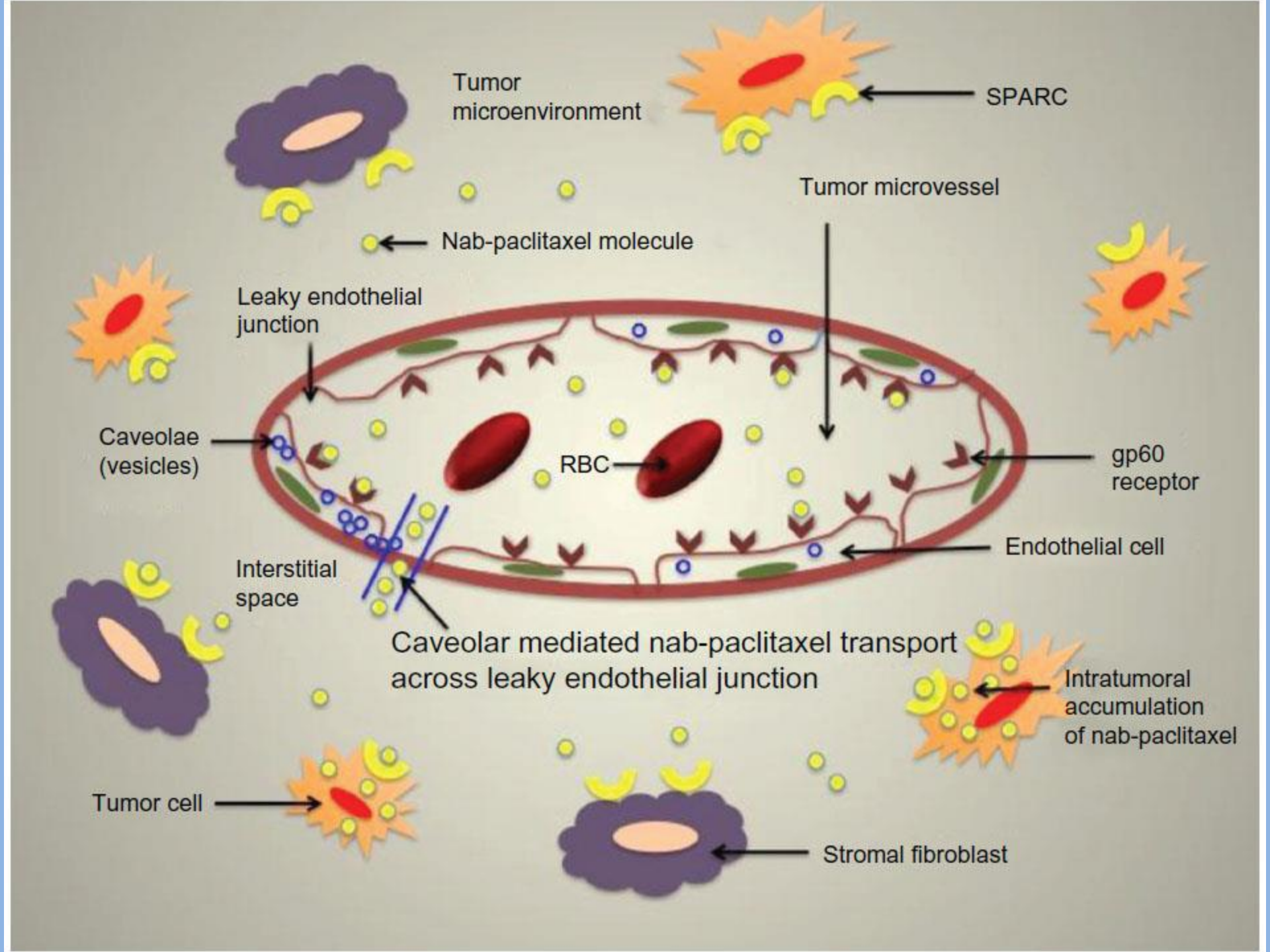


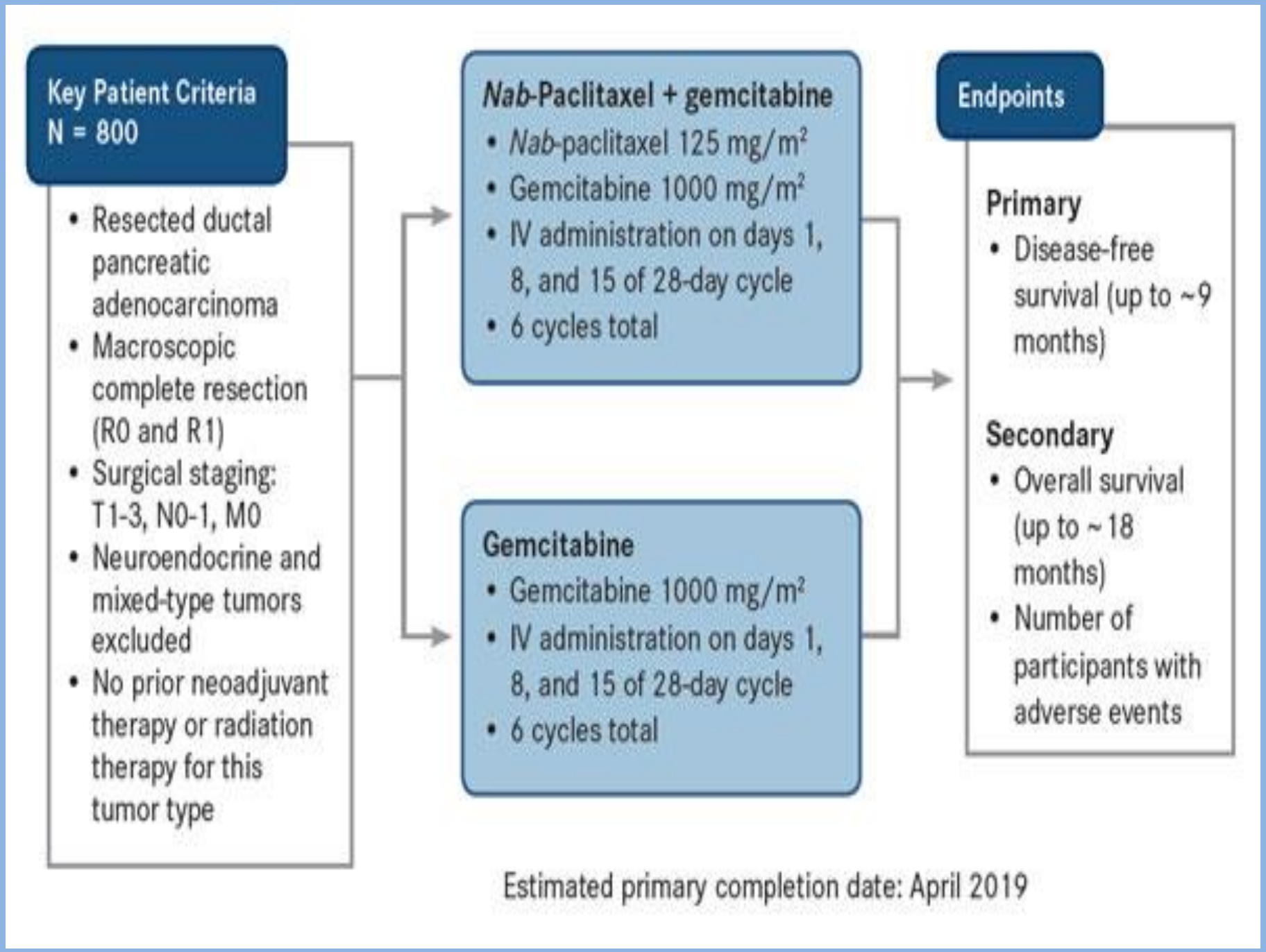
Gabizon et al., Cancer Res. 1994

DOXIL Clinical Proofs of Added Value

- **Cardiac function:** Major reduction of cardiotoxicity as compared to free doxorubicin in all settings. (2000)
- **AIDS-related Kaposi's Sarcoma:** Superior efficacy over former conventional therapy (1995)
- **Recurrent Ovarian Cancer**: Superior efficacy and improved safety profile over comparator drug (topotecan) (1998)
- **Metastatic Breast Cancer:** Equivalent efficacy and reduced cardiotoxicity compared to free doxorubicin (2003)
- **Multiple Myeloma:** Equivalent efficacy and improved safety profile compared to free doxorubicin combo. Superior efficacy in combination with bortezomib over single agent bortezomib. (2007)


Albumin
130 nm
Paclitaxel molecule
Nab-paclitaxel

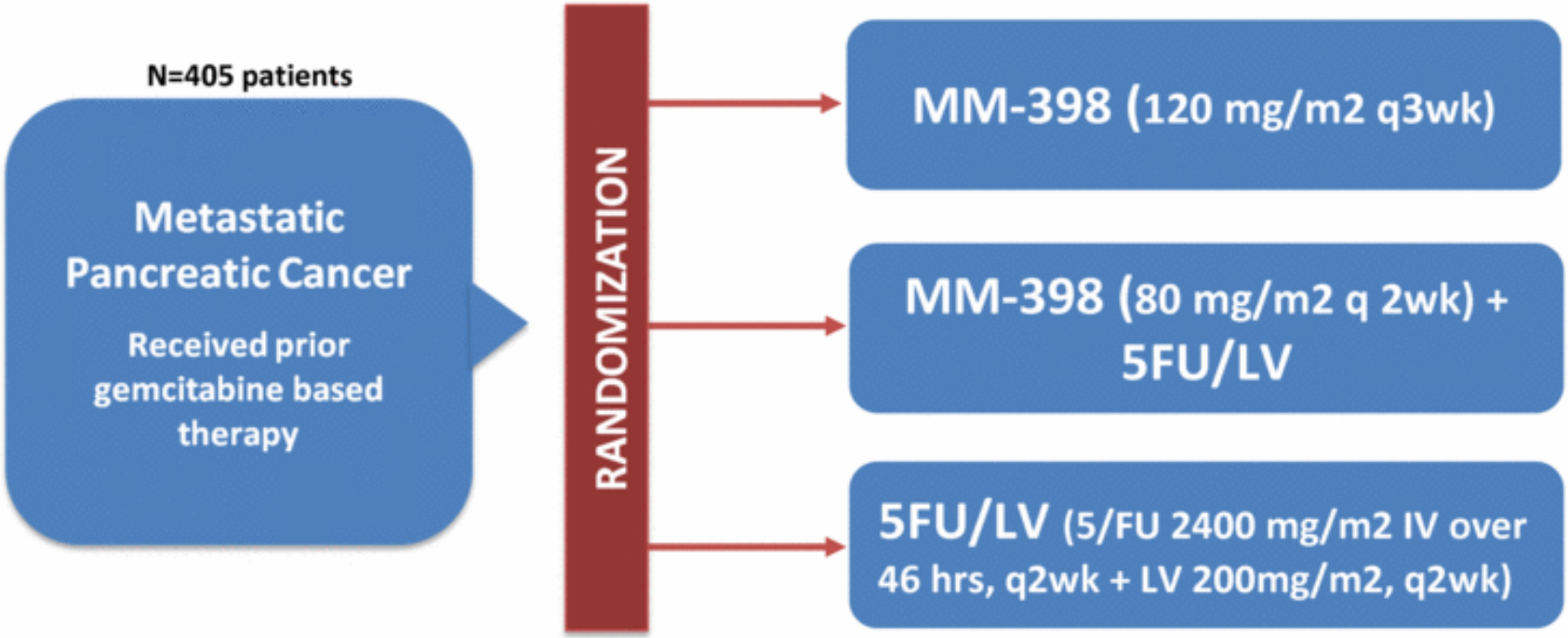

Tumor microenvironment
SPARC
Tumor microvessel
Nab-paclitaxel molecule
Leaky endothelial junction
Caveolae (vesicles)
RBC
gp60 receptor
Endothelial cell
Interstitial space
Caveolar mediated nab-paclitaxel transport across leaky endothelial junction
Intratumoral accumulation of nab-paclitaxel
Tumor cell
Stromal fibroblast


Key Patient Criteria
N = 800
• Resected ductal pancreatic adenocarcinoma
• Macroscopic complete resection (R0 and R1)
• Surgical staging: T1-3, N0-1, M0
• Neuroendocrine and mixed-type tumors excluded
• No prior neoadjuvant therapy or radiation therapy for this tumor type
Nab-Paclitaxel + gemcitabine
• Nab-paclitaxel 125 mg/m²
• Gemcitabine 1000 mg/m²
• IV administration on days 1, 8, and 15 of 28-day cycle
• 6 cycles total
Gemcitabine
• Gemcitabine 1000 mg/m²
• IV administration on days 1, 8, and 15 of 28-day cycle
• 6 cycles total
Endpoints
Primary
• Disease-free survival (up to ~9 months)
Secondary
• Overall survival (up to ~18 months)
• Number of participants with adverse events
Estimated primary completion date: April 2019

Phase 3 Pancreatic Study Design

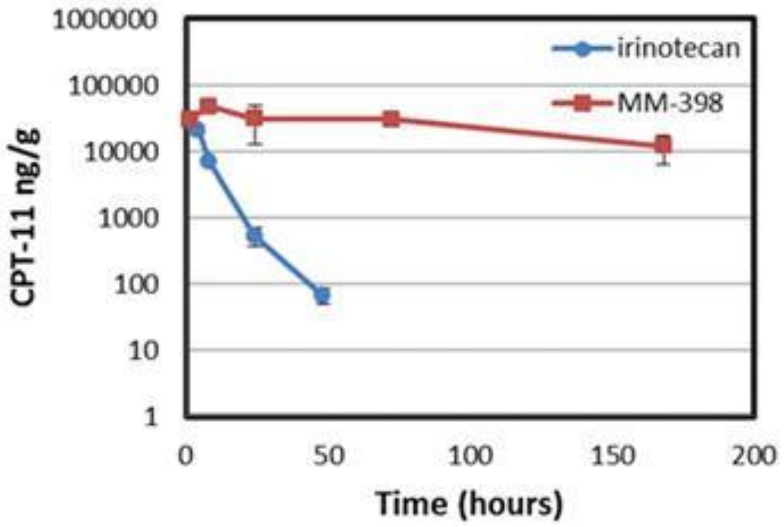
- Trial designed to determine the efficacy and safety of MM-398 alone or in combination with 5FU/LV versus an infusion of 5FU/LV
- Study design reviewed by US FDA and EMEA; plan to file for mono and/or combination arms with met endpoints
- Primary endpoint: OS (4.5 mos mono, 6 mos combo vs 3 mos control)

NAPOLI-1 (NAnoliPOsomaL Irinotecan) Trial



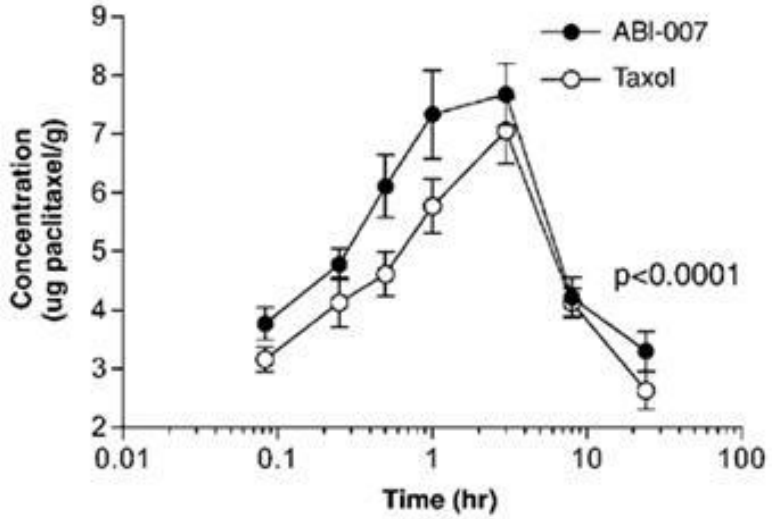
MM-398 Increases the Amount of Active Drug Available at the Tumor Site Compared to Other Encapsulated Agents *In Vitro*

MM-398: Sustained intra-tumor levels



	$t_{1/2}$ (h)	AUC_∞ (µg*h/ml)
CPT-11	.27	6
MM-398	10.7	2134

Abraxane® intra-tumor levels



Desai et al. (2006) Clin Cancer Res 12, 1317-1324.

	$t_{1/2}$ (h)	AUC_∞ (µg*h/ml)
Taxol	7.24	5.85
Abraxane	11.42	4.59

MM-398

- Nanotherapeutic encapsulation of irinotecan
- Engineered for increased drug deposition, local activation of SN38, and prolonged cytotoxic effects
- Diagnostic approach: utilize imaging agent to identify responders
- Taiwan Partner: PharmaEngine

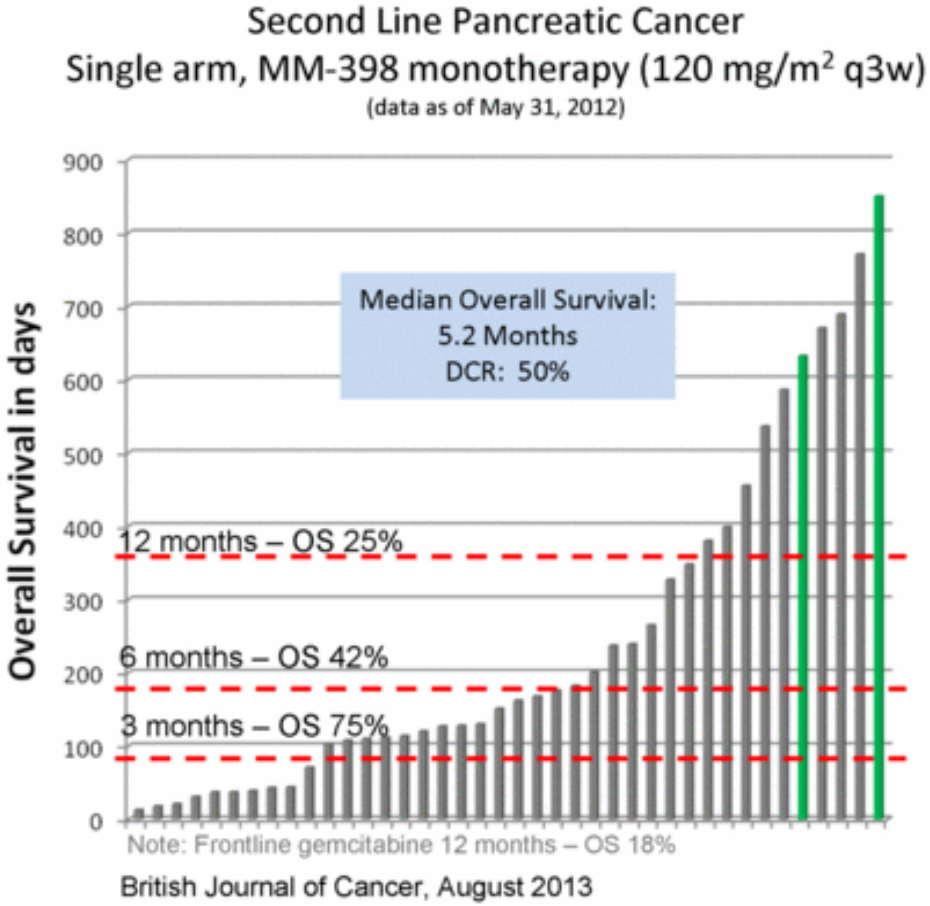
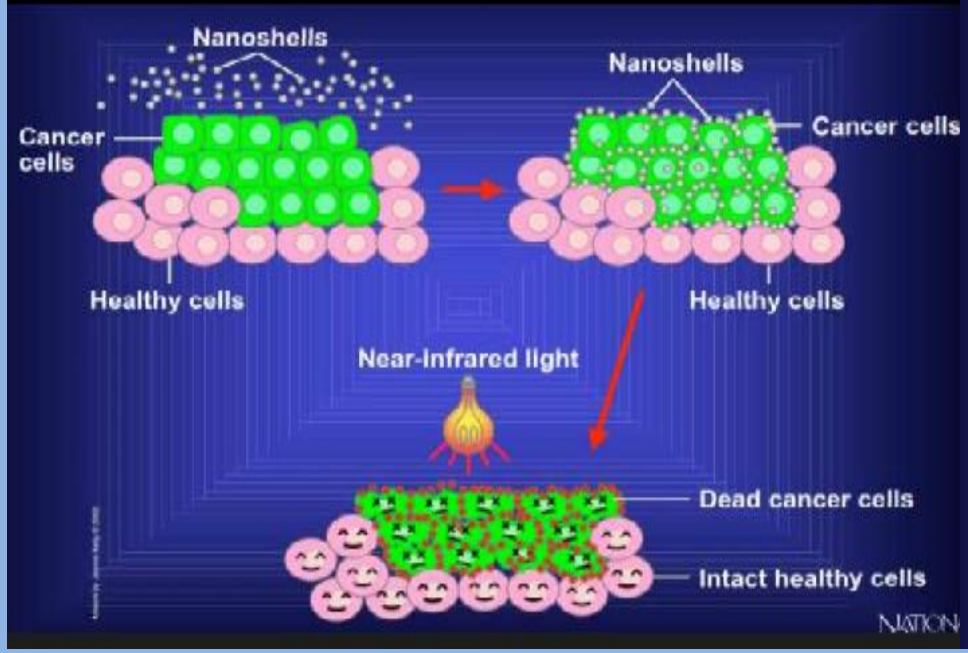


Table 1. Nanoparticle Formulations of Anticancer Therapies Approved in the United States and/or Europe

Name	Vehicle	Indication	Where Approved
Pegylated liposomal doxorubicin	Pegylated liposomes	AIDS-related Kaposi sarcoma; after failure of, or in cases of intolerance of, prior systemic chemotherapy	US, Europe
		Multiple myeloma; in combination with bortezomib in patients who have not previously received bortezomib and who have received at least 1 prior therapy	US, Europe
		Advanced ovarian cancer; after failure of platinum-based chemotherapy	US, Europe
		Metastatic breast cancer; where there is an increased cardiac risk associated with conventional doxorubicin	Europe only
Liposomal doxorubicin	Nonpegylated liposomes	Previously untreated metastatic breast cancer; in combination with cyclophosphamide	Europe only
Liposomal daunorubicin	Nonpegylated liposomes	Advanced AIDS-related Kaposi sarcoma; as first-line cytotoxic therapy	US only
Liposomal cytarabine	Nonpegylated liposome matrix	Lymphomatous meningitis; for intrathecal use only	US, Europe
Liposomal vincristine	Nonpegylated liposomes	Relapsed Philadelphia chromosome–negative acute lymphoblastic leukemia	US only
Nab-paclitaxel	Nanoparticles of albumin-bound drug conjugates	Metastatic breast cancer; after failure of combination chemotherapy for metastatic disease, or in cases of relapse within 6 months of adjuvant chemotherapy	US, Europe
		Locally advanced or metastatic non–small-cell lung cancer; with carboplatin, as first-line treatment	US, Europe
		Metastatic pancreatic adenocarcinoma; with gemcitabine, as first-line treatment	US, Europe
Nanoliposomal irinotecan	Pegylated liposomes	Metastatic pancreatic adenocarcinoma; with fluorouracil and leucovorin, after progression following gemcitabine-based therapy	US, Europe
Liposomal mifamurtide	Nonpegylated liposomes	High-grade resectable nonmetastatic osteosarcoma; after macroscopically complete surgical resection	Europe only

Nanoshells as Cancer Therapy

- Researchers can already link nanoshells to antibodies that recognize cancer cells.
- In laboratory cultures, the heat generated by the light-absorbing nanoshells has successfully killed tumor cells while leaving neighboring cells intact.



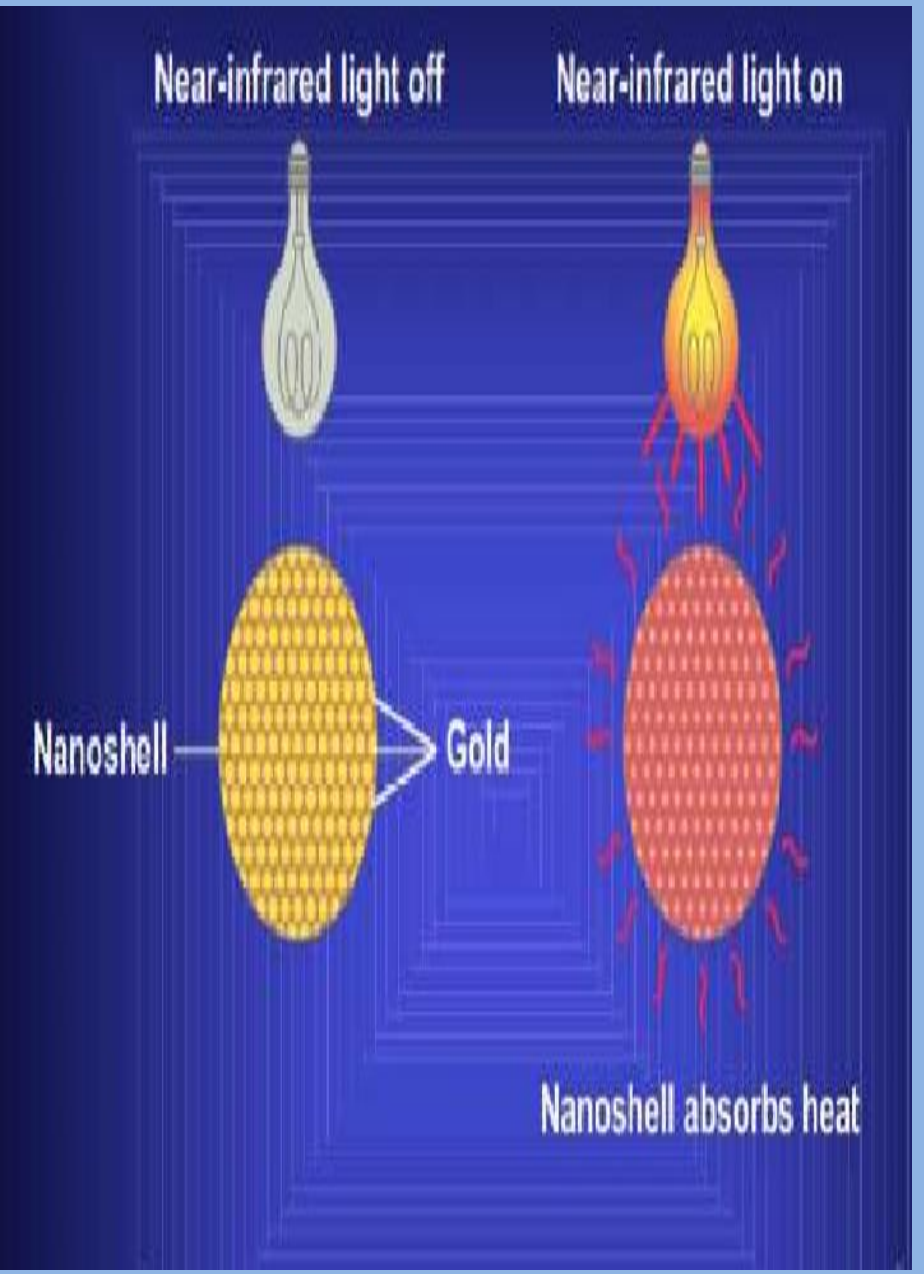
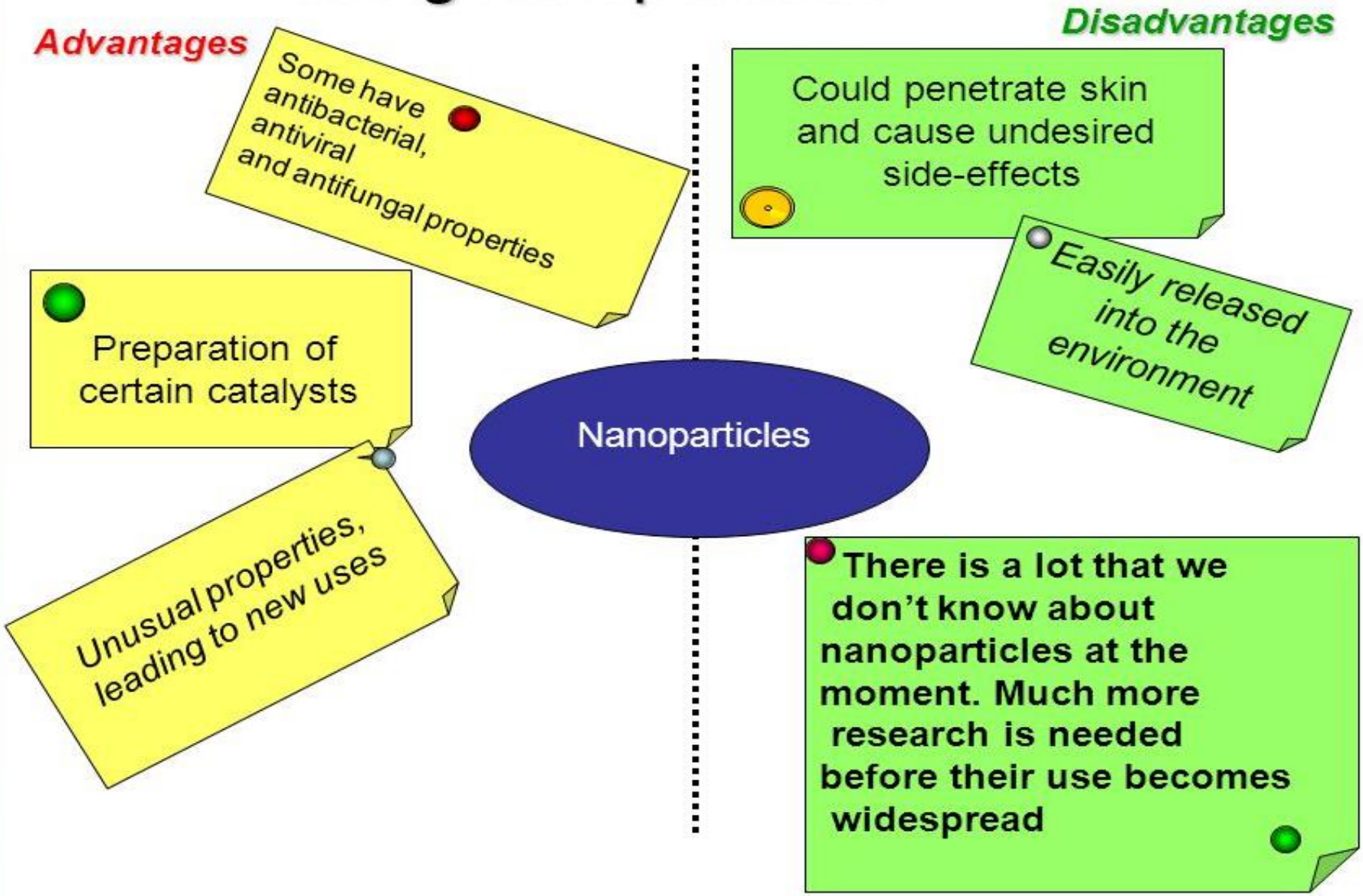


Table 2. Selected Nanoparticle Formulations in Clinical Trials for Cancer Therapy

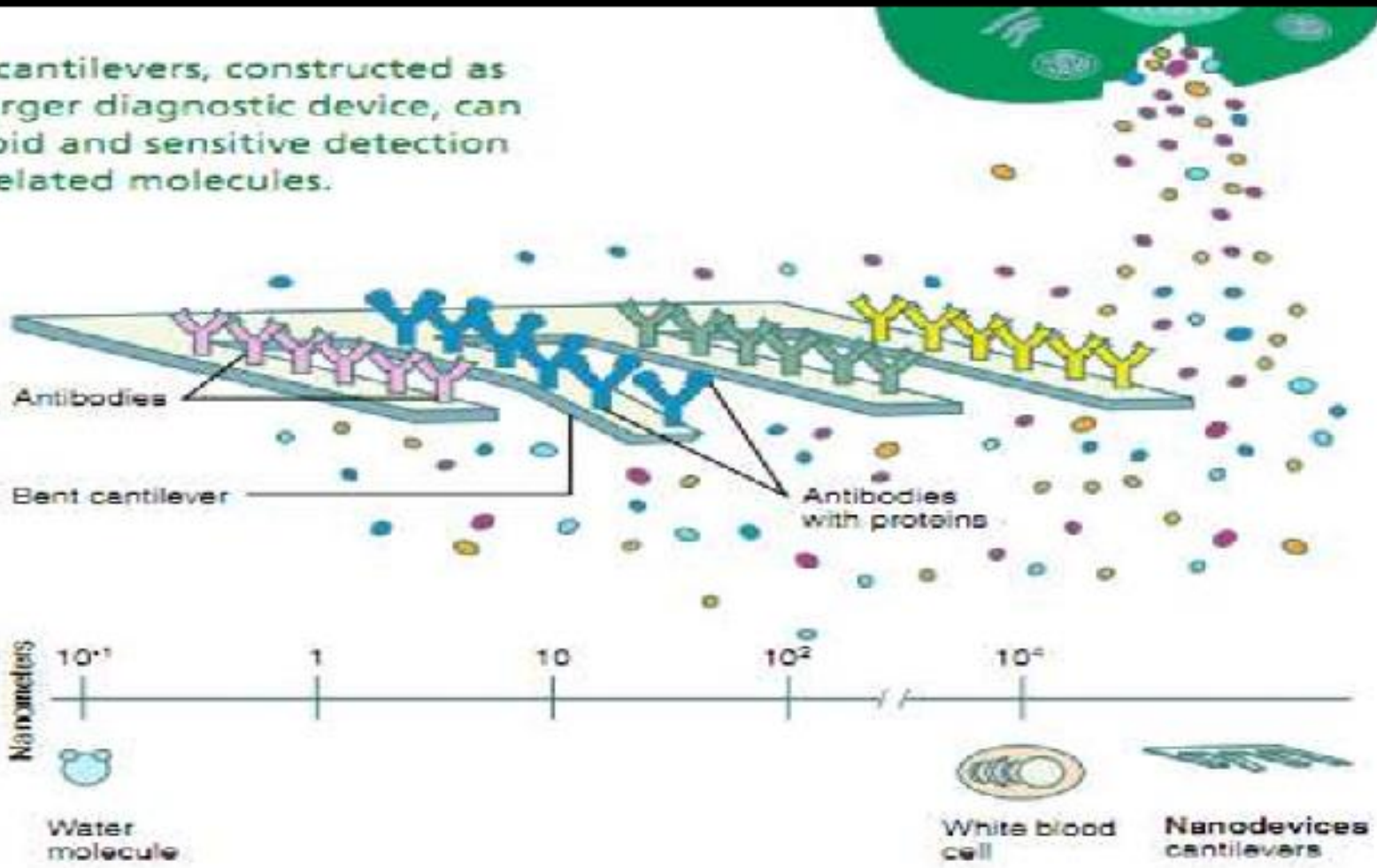
Drug Name	Vehicle	Active Therapeutic	Clinical Trials
LIPOSOMAL AGENTS			
Lyso-thermosensitive liposomal doxorubicin (LTLD)	Pegylated temperature-sensitive liposome that forms pores, speeding drug release at 39–42°C	Doxorubicin	Phase III randomized trial: combined with radiofrequency ablation in hepatocellular carcinoma with solitary lesions (NCT02181556)
			Phase I trial: combined with focused ultrasound to induce tumoral hyperthermia in primary or secondary liver tumors (NCT02181075)
			Phase II trial: combined with RT and superficial hyperthermia in locally relapsed breast cancer (NCT02850419)
			Phase I trial: combined with magnetic resonance high-intensity focused ultrasound in pediatric refractory solid tumors (NCT02536183)
CPX-351	Liposome	Cytarabine and daunorubicin	Phase II trial: in newly diagnosed AML at high risk of induction mortality (NCT02286726)
			Phase I/II trial: combined with fludarabine, cytarabine, and G-CSF in children with relapsed AML (NCT02642965)
Pegylated liposomal mitomycin C lipid-based prodrug	Pegylated liposome	Lipid-based prodrug of mitomycin C	Phase I trial: in advanced solid tumors (NCT01705002); and phase IB trial: combined with capecitabine in metastatic colorectal cancer (NCT01705002)
Liposomal mitoxantrone hydrochloride	Pegylated liposome	Mitroxantrone	Phase I/II trial: in relapsed/refractory non-Hodgkin lymphoma (NCT02856685)
			Phase II trial: in metastatic breast cancer (NCT02596373)
			Phase II trial: in relapsed DLBCL and peripheral NK/T-cell lymphoma (NCT02597387)
LiPlaCis	Pegylated liposome, with release activated by tissue expression of phospholipase A2 (PLA2)	Cisplatin	Phase I trial: in advanced solid tumors (NCT01861496)
Anti-EGFR immunoliposomes	Pegylated liposome covalently linked to antigen-binding fragments of cetuximab	Doxorubicin	Phase II trial: in advanced triple-negative EGFR-positive breast cancer (NCT02833766)
MM-302	Pegylated liposome conjugated to single-chain anti-HER2 antibodies (scFv)	Doxorubicin	Phase II/III trial: combined with trastuzumab, compared with physician's choice of chemotherapy for advanced HER2-amplified breast cancer after prior treatment with trastuzumab, ado-trastuzumab emtansine, and pertuzumab (NCT02213744); terminated following futility analysis
PROTEIN-DRUG CONJUGATES			
Nanoparticle albumin-bound rapamycin (ABI-009)	Nanoparticle albumin-bound	Rapamycin (mTOR inhibitor)	Phase II trial: in metastatic solid tumors with mTOR pathway aberrations (NCT02646319)
			Phase II trial: in advanced malignant PEComa (NCT02494570)
			Phase I/II trial: in non–muscle-invasive bladder cancer (NCT02009332)
POLYMERIC NANOPARTICLES			
Nanoparticle camptothecin (CRLX101)	Cyclodextrin-PEG copolymer conjugated to drug; self-assembles into 30- to 40-nm nanoparticles	Camptothecin (topoisomerase 1 inhibitor)	Phase I/II trial: combined with olaparib in relapsed/refractory small-cell lung cancer (NCT02769962)
			Phase I/II trial: combined with paclitaxel in ovarian, fallopian tube, or primary peritoneal cancer (NCT02389985)
			Phase I trial: as monotherapy or combined with bevacizumab or with mFOLFOX6 in solid cancers (NCT02648711)
			Phase I/II trial: combined with capecitabine and RT as neoadjuvant treatment of rectal cancer (NCT02010567)
CRLX301	Cyclodextrin-PEG copolymer conjugated to drug; self-assembles into nanoparticles	Docetaxel	Phase I trial: in solid cancers (NCT02380677)
Doxorubicin Transdrug	Polyisohexylcyanoacrylate nanoparticles	Doxorubicin	Phase III trial: in advanced hepatocellular carcinoma (NCT01655693)
POLYMERIC MICELLES			
Docetaxel micelle	Pegylated core-crosslinked polymeric micelles	Docetaxel	Phase I trial: in solid cancers (NCT02442531)
NC-6004	Pegylated polymeric micellar nanoparticles, with coordination bonds between platinum drug and polymers	Cisplatin	Phase I/II trial: combined with gemcitabine in non–small-cell lung, biliary tract, and bladder cancers (NCT02240238)
			Phase III randomized trial: combined with gemcitabine, vs gemcitabine alone, in locally advanced or metastatic pancreatic cancer (NCT02043288)
			Phase I trial: combined with 5-FU and cetuximab in metastatic head and neck squamous cell carcinoma (NCT02817113)
Diaminocyclohexane (DACH)-platin micelle (NC-4016)	Pegylated polymeric micellar nanoparticles, with coordination bonds between platinum drug and polymers	DACH-platin (active metabolite of oxaliplatin)	Phase I trial: in advanced solid cancers or lymphoma (NCT01999491)
Epirubicin micelle (NC-6300/K-912)	pH-sensitive pegylated polymeric micelle	Epirubicin	Phase I trial: in advanced solid tumors (JapicCTI-132221)
DENDRIMER-DRUG CONJUGATES			
Dendrimer-docetaxel (DTX-SPL8783)	Pegylated polylysine dendrimers	Docetaxel	Phase I trial: in advanced solid tumors (ACTRN12614000171617)
DNA/RNA/OLIGONUCLEOTIDE DELIVERY			
SGT-53	Cationic liposome with antitransferrin receptor antibody fragment on surface	*TP53* cDNA in a plasmid backbone	Phase II trial: combined with gemcitabine and nab-paclitaxel in metastatic pancreatic cancer (NCT02340117)
			Phase I trial: as monotherapy and combined with cyclophosphamide and topotecan in children (NCT02354547)
			Phase II trial: combined with temozolomide in glioblastoma multiforme (NCT02340156)
MTL-CEBPA	Liposomal nanoparticle	Small activating RNA to restore *CEBPA*	Phase I trial: in advanced hepatocellular carcinoma (NCT02716012)
***FUS1* nanoparticle**	DOTAP:cholesterol nanoparticles	*FUS1* expression plasmid	Phase I/II trial: combined with erlotinib in stage IV non–small-cell lung cancer (NCT01455389)
siRNA-EphA2	DOPC liposome	siRNA targeting degradation of *EphA2*	Phase I trial: in advanced solid tumors (NCT01591356)
BP1001	Liposome	*Grb2* antisense oligonucleotide	Phase II trial: combined with low-dose cytarabine in AML patients who cannot tolerate induction therapy (NCT02781883)

Advantages and disadvantages of using nanoparticles

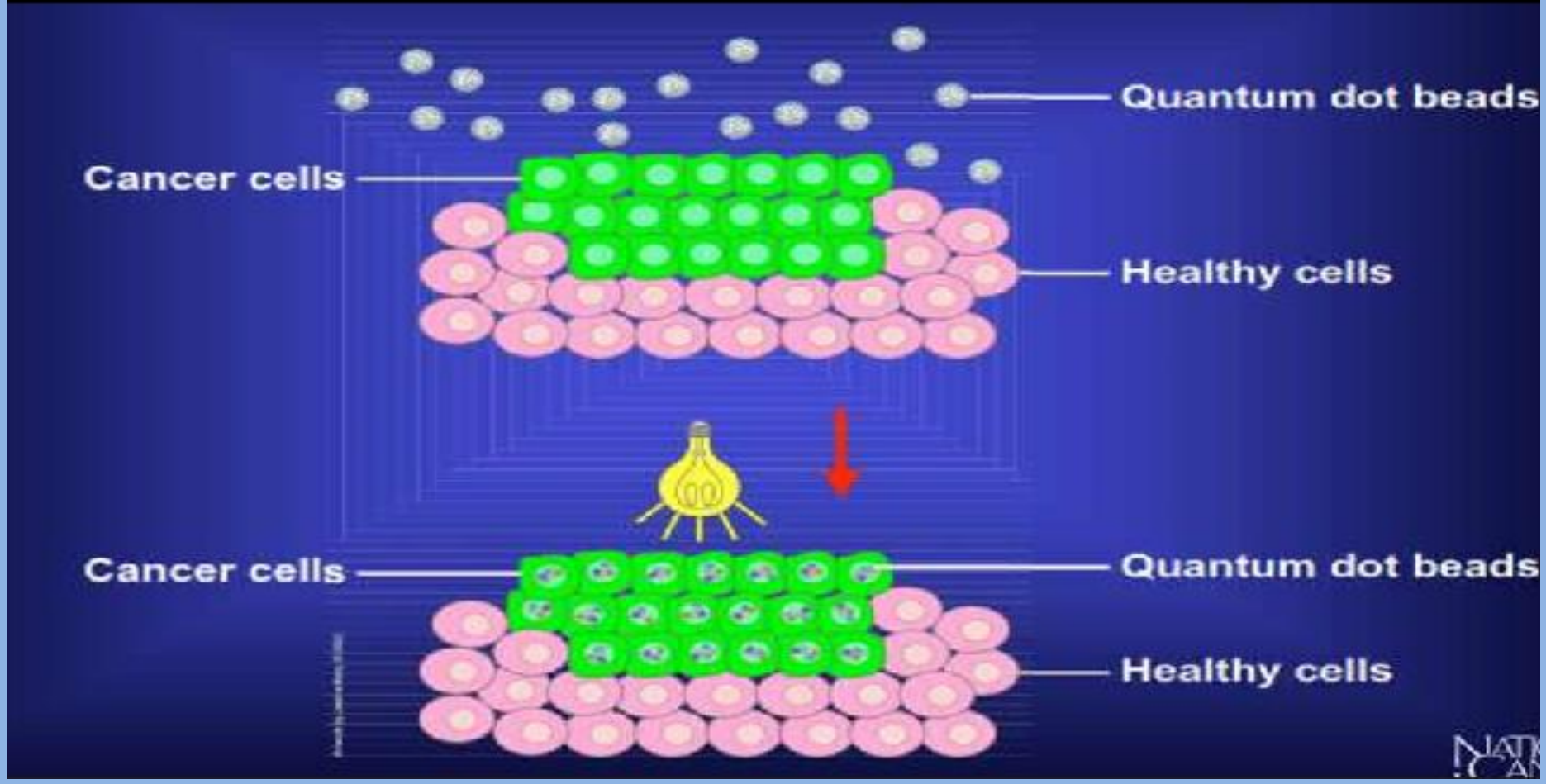


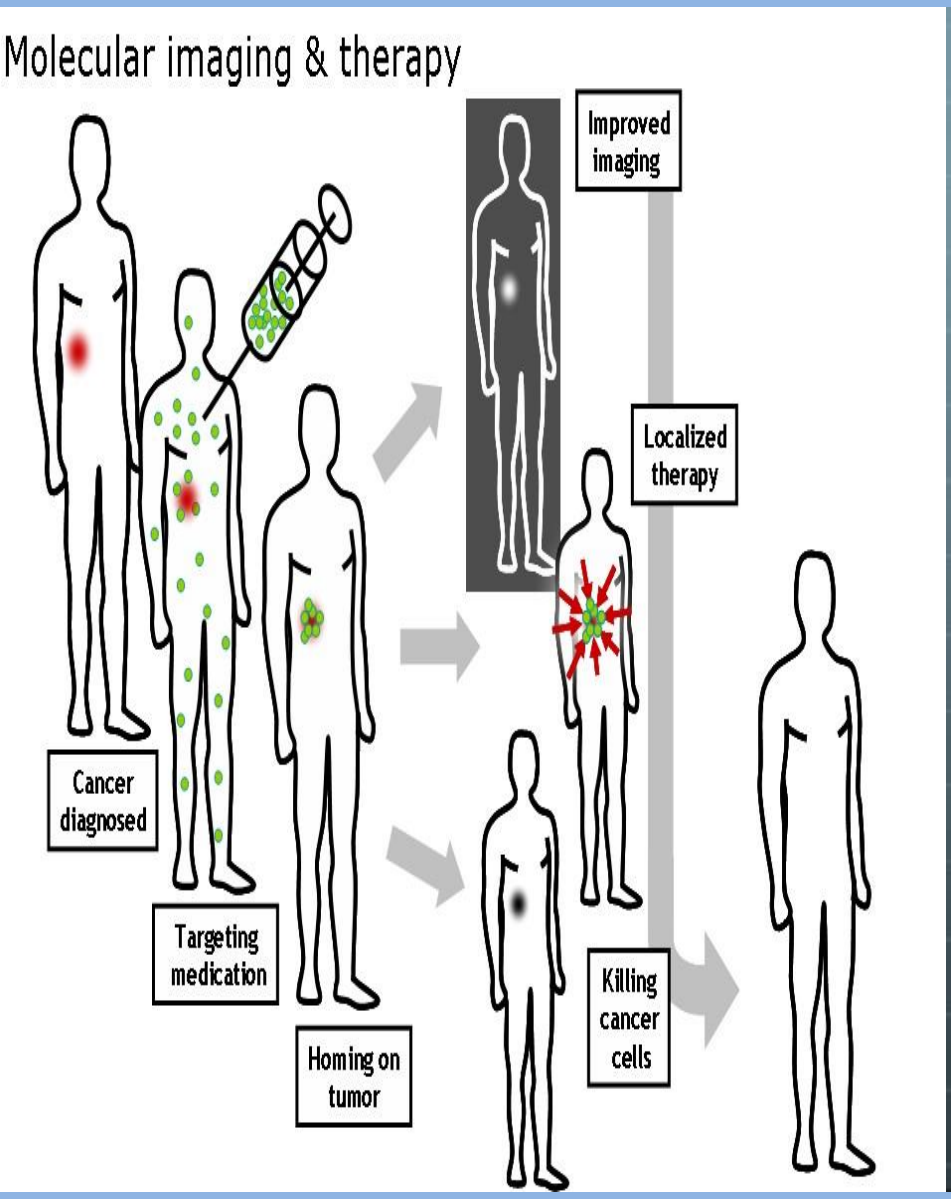
Cantilevers Can Make Cancer Tests Faster and More Efficient

Nanoscale cantilevers, constructed as part of a larger diagnostic device, can provide rapid and sensitive detection of cancer-related molecules.



Quantum Dots Can Find Cancer Signatures





Nanotechnology in medicine

- The ability to manipulate structures and properties at the nanoscale in medicine is like having a sub-microscopic lab bench on which you can handle cell components, viruses or pieces of DNA, using a range of tiny tools, robots and tubes.
- Chemists at New York University (NYU) have created a nanoscale robot from DNA fragments that walks on two legs just 10 nm long.
- The genesis of nanotechnology can be traced to the promise of revolutionary advances across medicine, communications, genomics and robotics.


Thank you