

TEL AVIV UNIVERSITY



אוניברסיטת תל-אביב

Medical Application - Nanomedicine

Prof. Rafi Korenstein

The Marian Gertner Institute for Nanomedical Systems
and Dept. of Physiology and Pharmacology
Sackler Faculty of Medicine

Nanomedicine

Definition - Diagnosis and therapy based on nanotechnology and nanoscience

Diagnostics

- **in-vivo** diagnostics (in-vivo imaging based on nanoscale contrast particles, implanted monitoring MEMS based sensors)

(imaging by e.g. MRI, f-MRI, ultrasound, RF, Holography)

- **in-vitro** diagnostics

("lab-on-chip", "cell-on-chip")

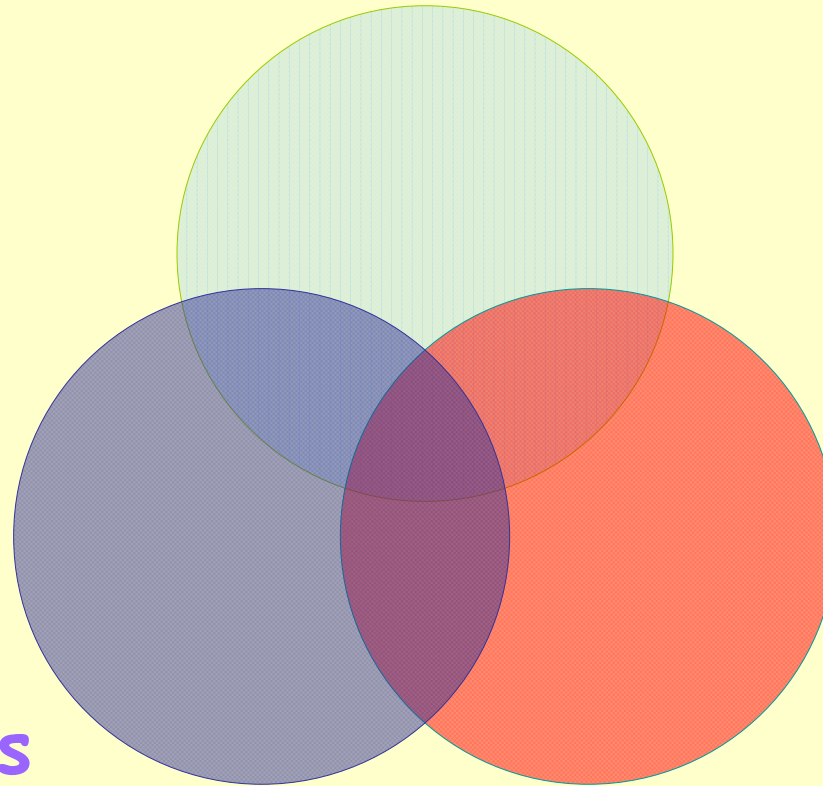
Nanomedicine

Therapeutics

- ✓ Targeted drug delivery (nanoparticles as drug carriers)
- Medical devices (smart stents, microneedles for electrical stimulation, MEMS based endoscopes, implantable drug release devices)
- Regenerative medicine (smart implants, cell based therapies)

Challenges of Nano-Mediated Drug Delivery

delivery routes



nanocarriers

targeting

Challenges in drug delivery

- Overcoming biological barriers
(intestine, air-blood barrier of the human lung, skin and blood-brain-barrier)
- Efficient nanocarriers
(high dosage of loading, release at the appropriate target-prodrug/drug, optimal pharmacokinetics)

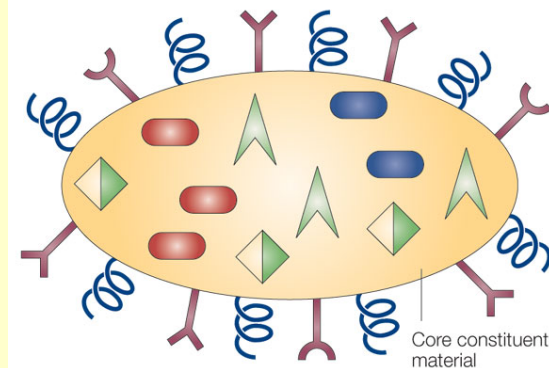
Challenges in drug delivery

- Improved targeting

Extracellular - membrane receptors and extracellular epitopes

Intracellular - intracellular receptors and epitopes)

→ multifunctional targeted drug delivery systems -
"magic bullet"



Therapeutic or imaging payload	Biological surface modifier
Drug A	PEG
Drug B	Targeting moieties
Contrast enhancer	
Permeation enhancer	

Overcoming biological barriers

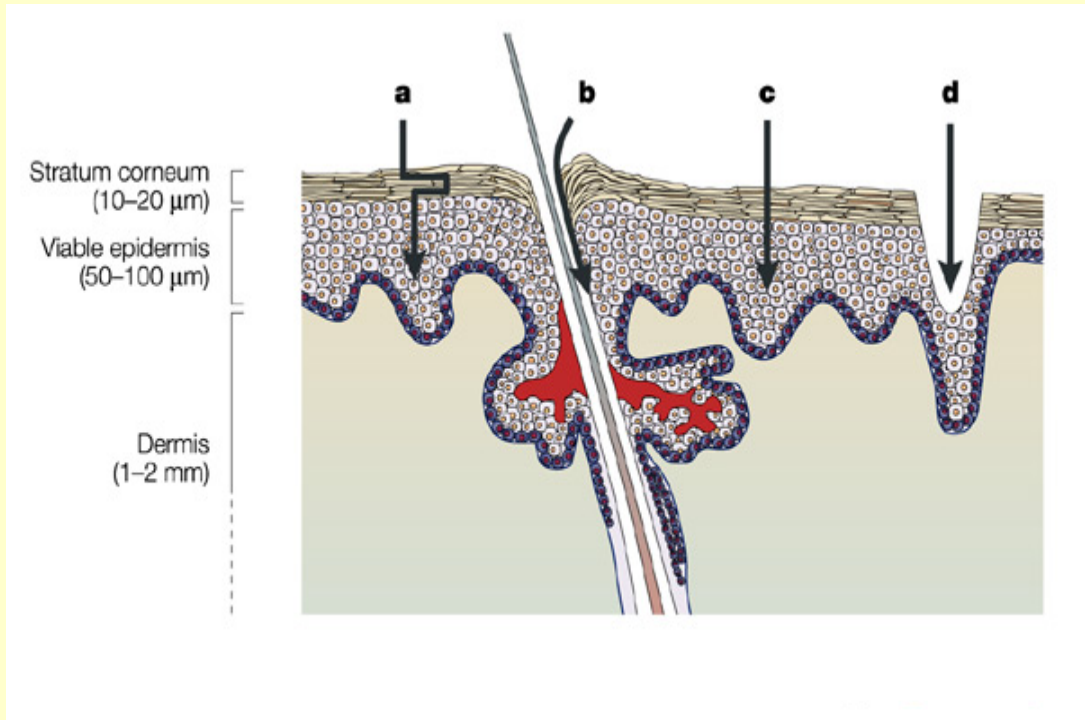
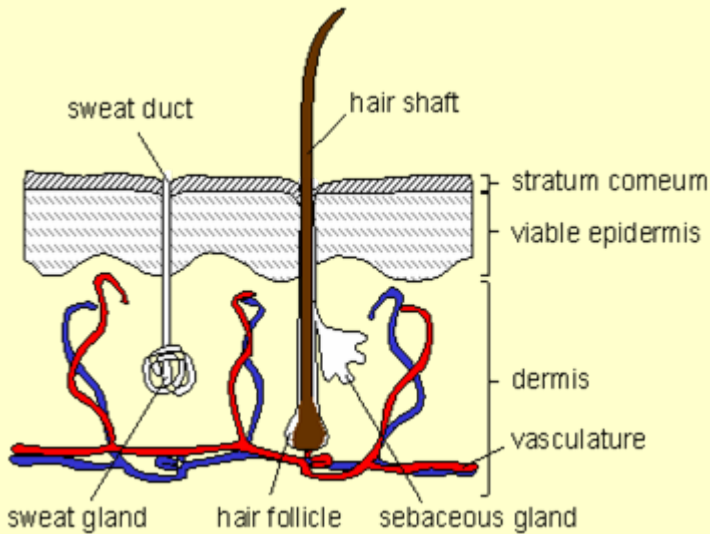
Drug Delivery Market

- 2006 Global DDS Market: ~\$88 Billion*

Delivery Route	2005	2006e*
Oral Enteral/ODT	41.1	46.4
Inhalation Pulmonary	14.0	16.0
Inhalation Nasal	3.4	3.7
Transdermal/Topical	7.1	7.7
Parenteral and Implant (PEGs, liposomes, depots, etc.)	11.0	12.9
Buccal/Sublingual Transmucosal	1.1	1.3
Other Transmucosal (vaginal, rectal, and ophthalmic)	0.3	0.4
Total	78.0	88.4

* Estimated for 2006 based on projections for actual 2005 sales

Transdermal drug delivery



Schematic representation of a cross section through human

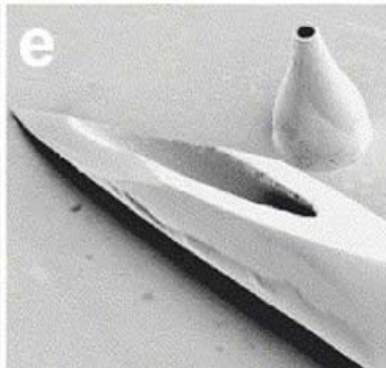
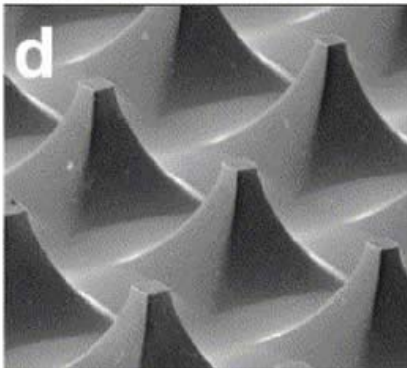
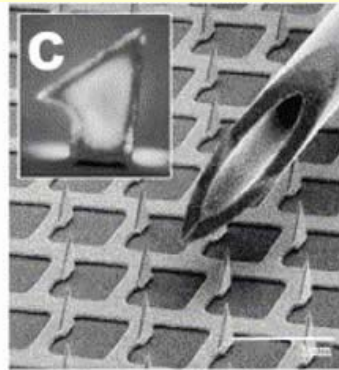
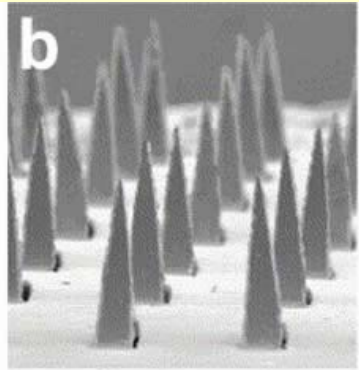
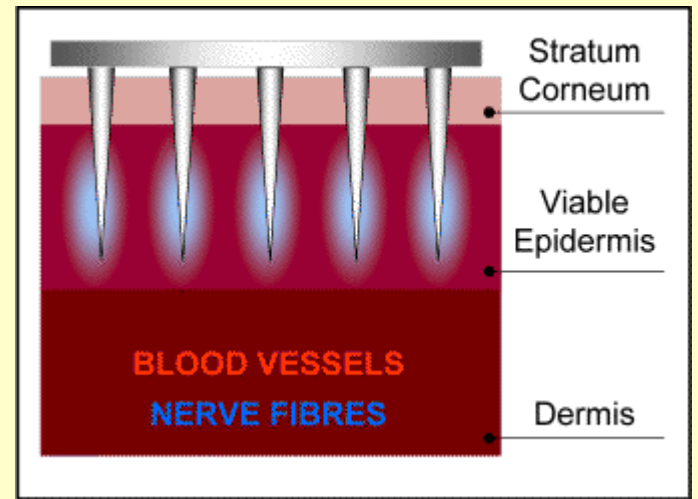


Table 2 | **Comparison of methods to enhance transdermal delivery***

Delivery method	Increased transport	Sustained delivery	No pain/irritation	Low cost/complexity
Hypodermic needle	XXX	XX	X	XXX
Chemical enhancers	X	XXX	XX	XXX
Iontophoresis	XX	XXX	XXX	X
Electroporation	XX	XXX	XX	X
Ultrasound	XX	XXX	XXX	X
Microneedles	XX	XXX	XXX	X
Jet injection	XXX	X	X	X
Thermal poration	XX	XXX	XXX	X

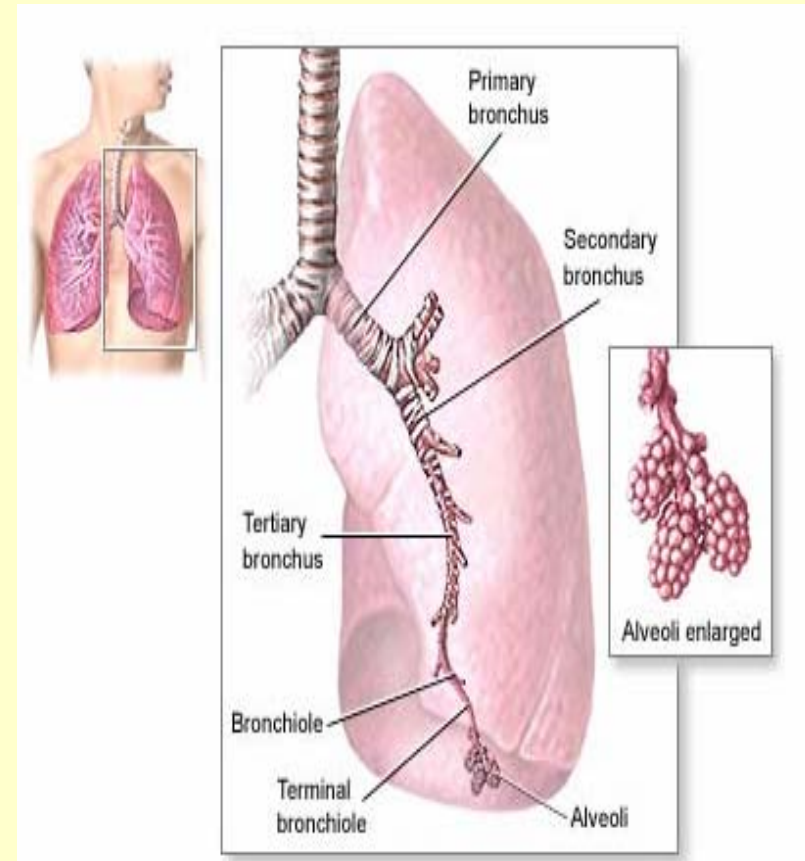
*Delivery methods are qualitatively compared on the basis of limited (X), moderate (XX) or good (XXX) efficacy in each category. These classifications are used to illustrate rough trends and are not intended to provide absolute rankings.

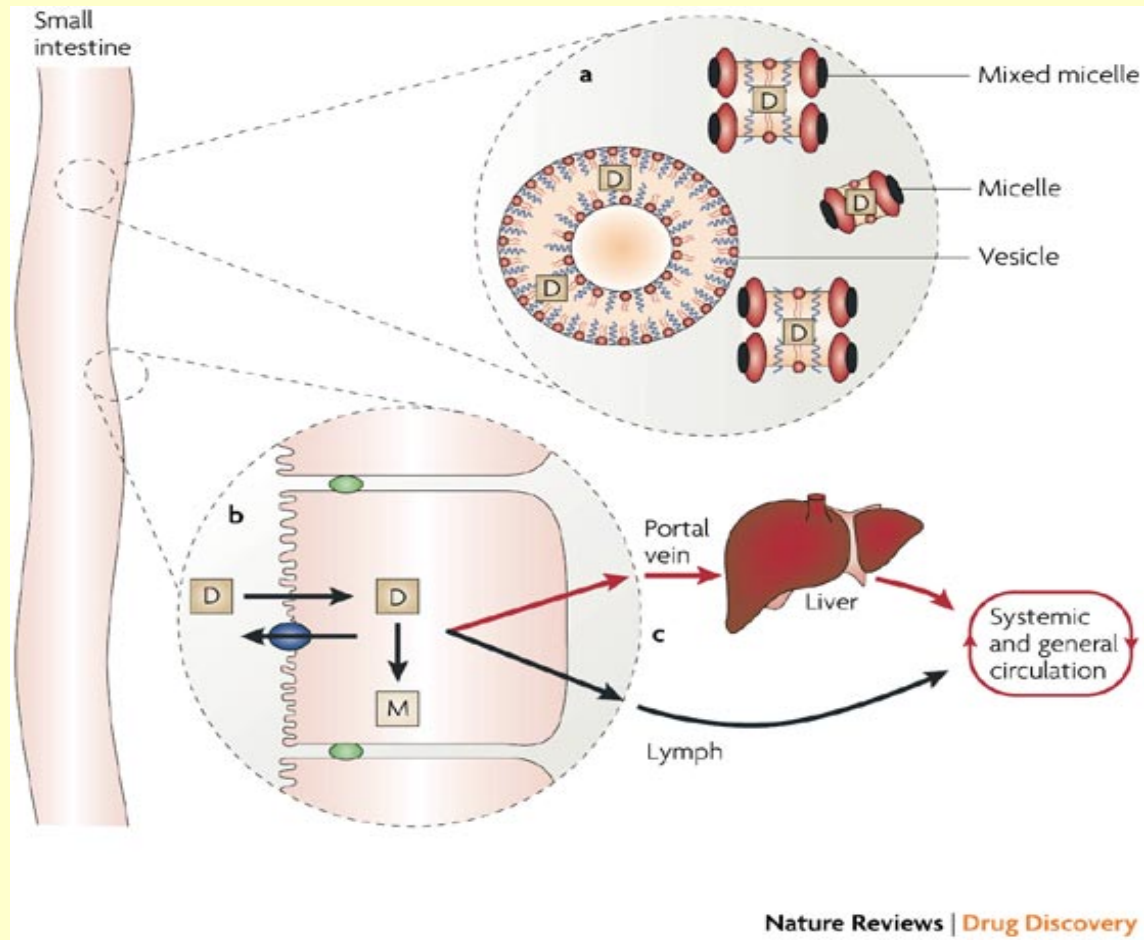
Pulmonary Administration Route

- Local delivery (e.g. vasoactive intestinal peptide (VIP) in asthma) size ~ 3 - 5 μm
- Systemic delivery (e.g. insulin in diabetes): size < 3 μm :

Main Barriers for Pulmonary Administration Route

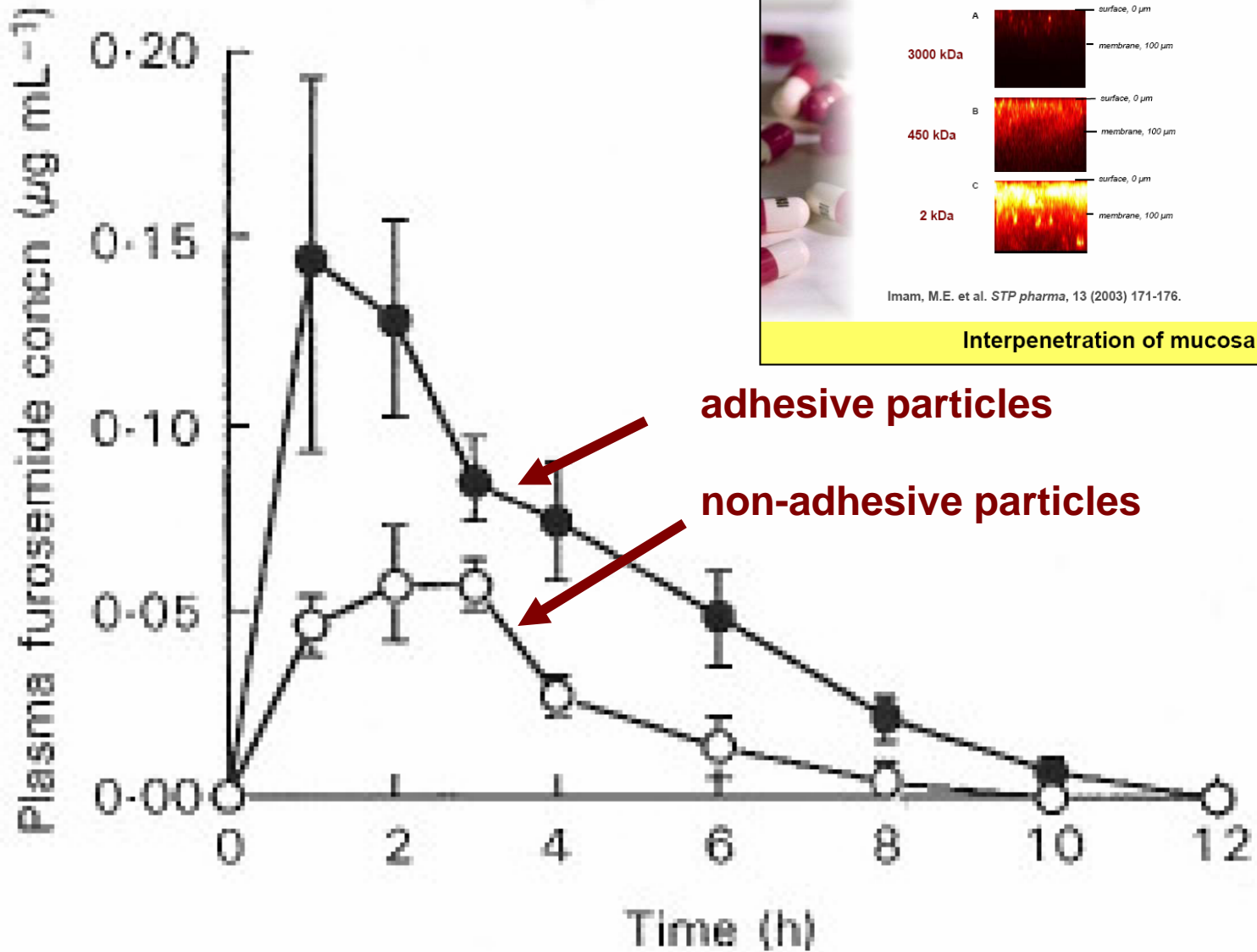
- Air-way geometry
- Clearance mechanisms
 - ✓ *mucociliary clearance*
 - ✓ *alveolar macrophages*
 - ✓ *metabolic activity of enzymes in the lung*
- Lung diseases
 - ✓ *mucus accumulation*
 - ✓ *alterations in lung architecture*





Porter *et al.* *Nature Reviews Drug Discovery* 6, 231–248 (March 2007)
 | doi:10.1038/nrd2197

Mucoadhesive Properties



Nano-carriers

Advantages of nanoparticles as drug carriers

- Large surface-to-volume ratio resulting enhanced interaction sites
- Surface functionalization for targeting
- Suitable encapsulation
- Release drugs in controlled manner
- More efficient uptake by cells

Summary of the two categories of nanoparticles according to application

Drug Delivery

- Polymeric nanoparticles
- Ceramic nanoparticles
- Polymeric micelles
- Dendrimer
- Liposomes

Imaging

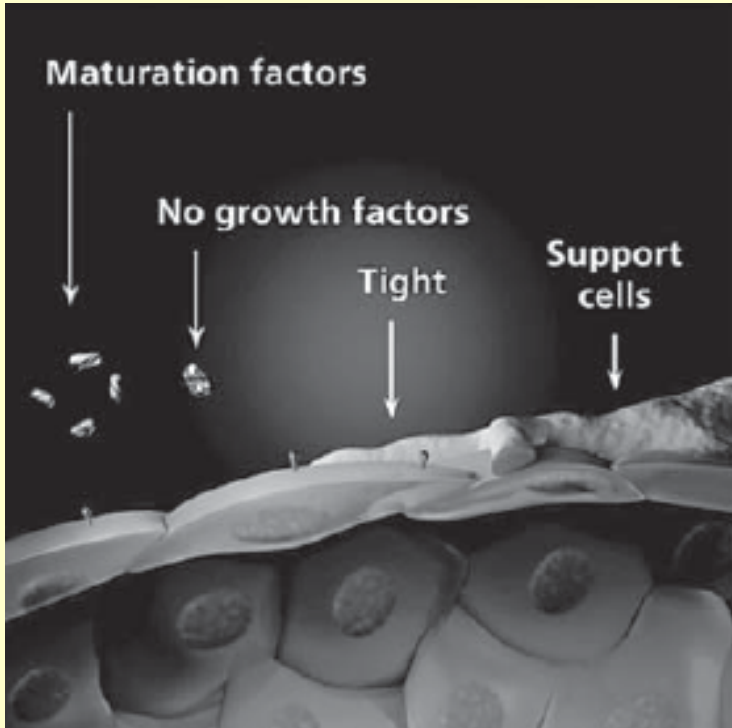
- Magnetic nanoparticles
- Quantum dots

Targeting

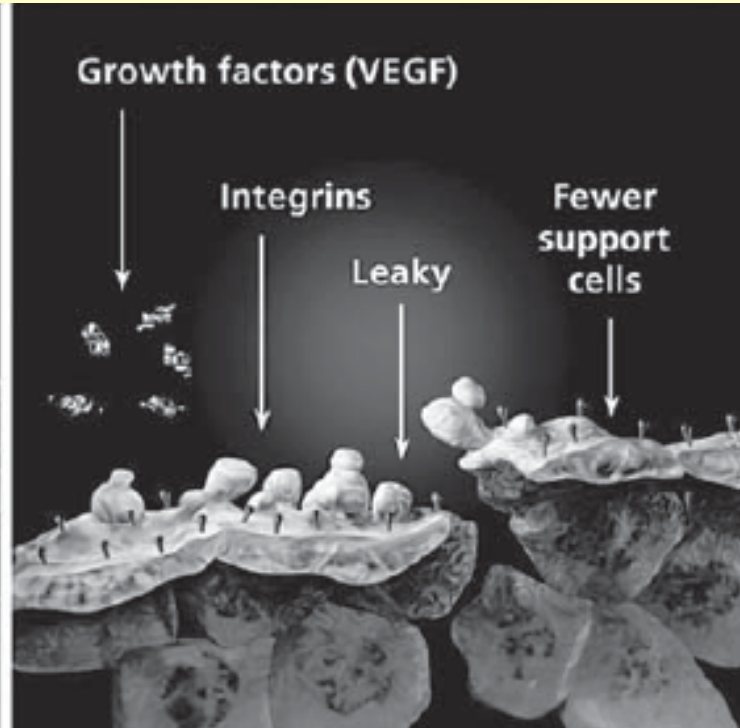


Enhanced extracellular
targeting in cancer

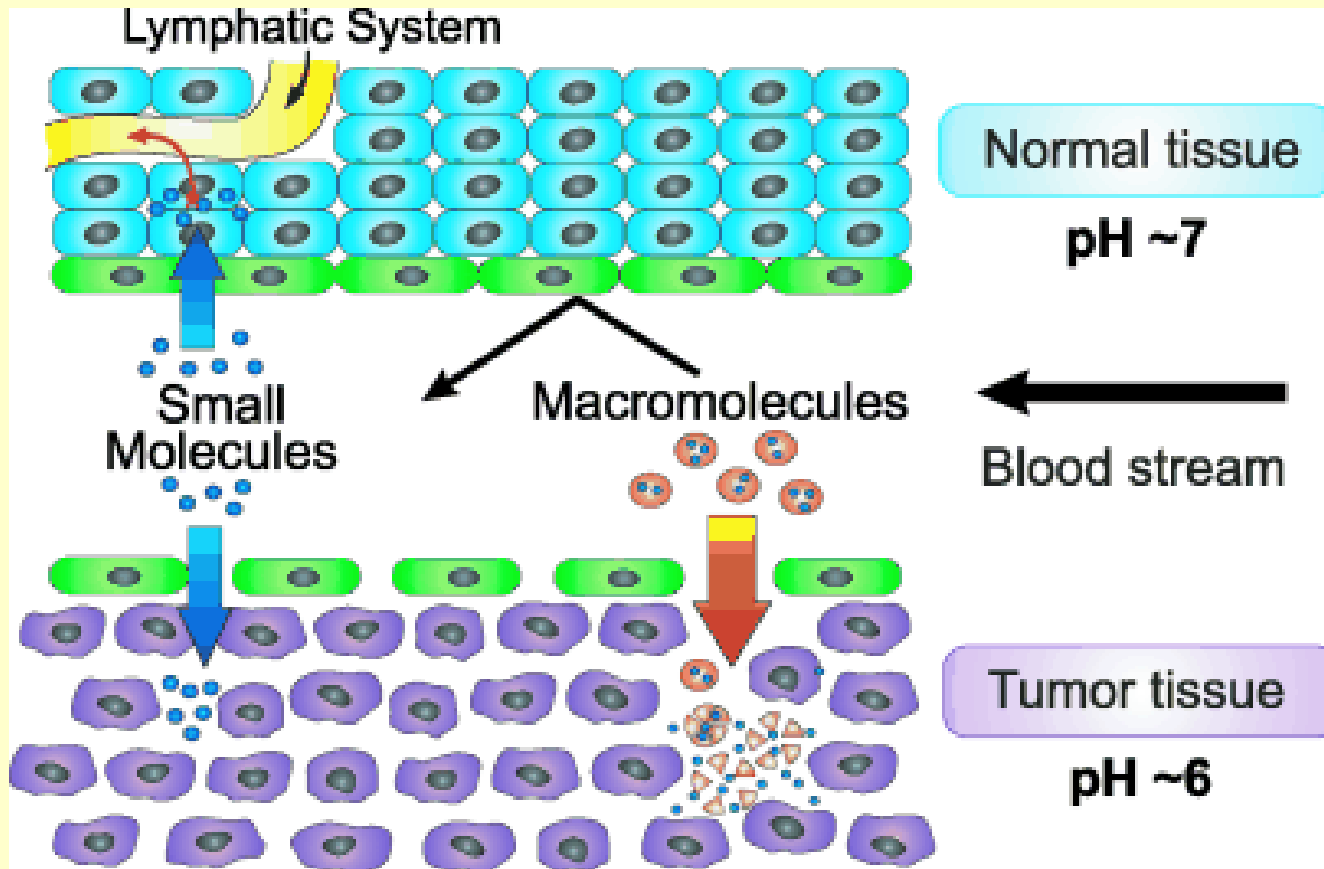
Normal blood vessels



Abnormal blood vessels



Enhanced permeability and Retention (EPR) Effect



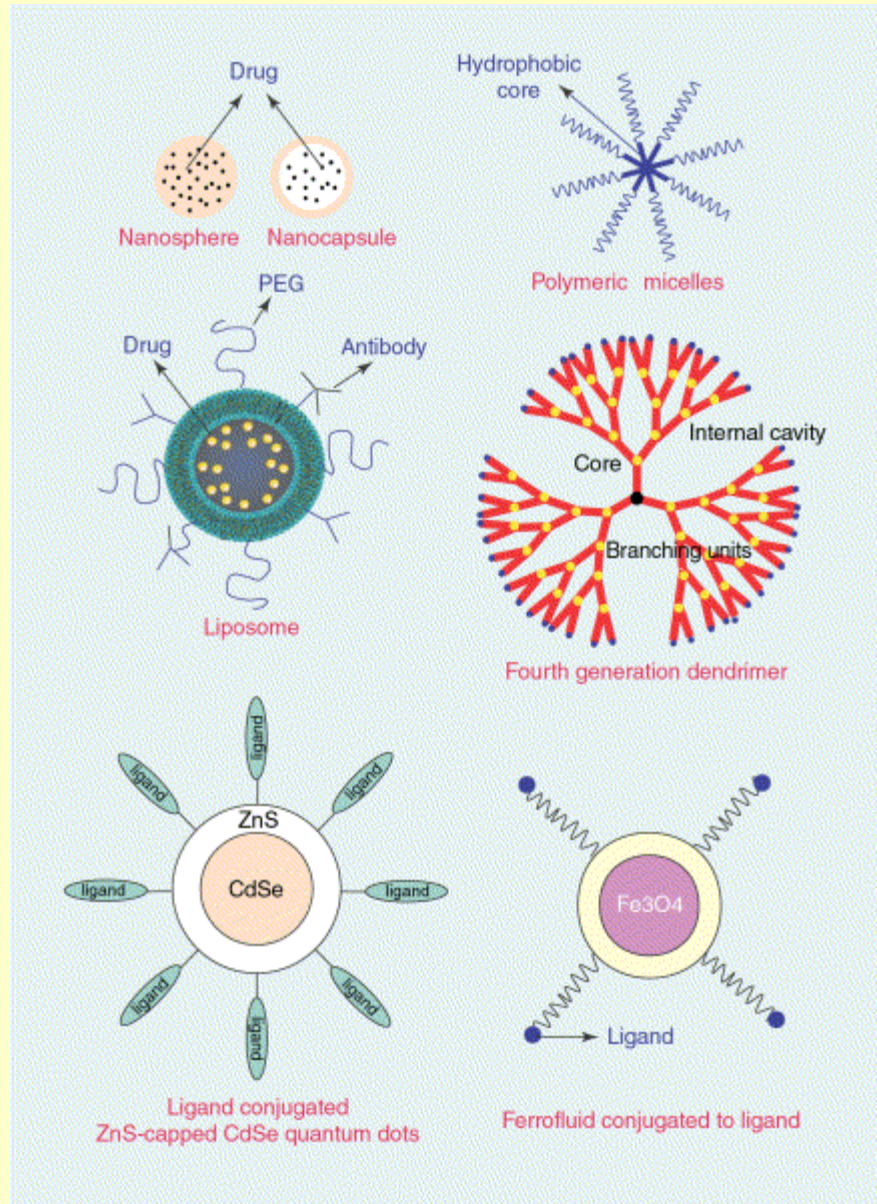
Polymer–drug conjugates

Compound	Name	Status	Indication	Refs
Polyglutamate–paclitaxel	CT-2103; Xyotax	Phase III	Various cancers, particularly non-small-cell lung cancer; ovarian cancer as a single agent or in combination therapy	107–111
Polyglutamate–camptothecin	CT-2106	Phase I	Various cancers	113
HPMA copolymer–doxorubicin	PK1; FCE28068	Phase II	Various cancers, particularly lung and breast cancer	88
HPMA copolymer–doxorubicin–galactosamine	PK2; FCE28069	Phase I/II	Particularly hepatocellular carcinoma	91
HPMA copolymer–paclitaxel	PNU166945	Phase I	Various cancers	93
HPMA copolymer–camptothecin	MAG-CPT	Phase I	Various cancers	95–97
HPMA copolymer–carboplatin platinite	AP5280	Phase I/II	Various cancers	99
HPMA copolymer–DACH–platinite	AP5346; ProLindac	Phase I/II	Various cancers	100
Dextran–doxorubicin	AD-70, DOX-OXD	Phase I	Various cancers	73
Modified dextran–camptothecin	DE-310	Phase I	Various cancers	74,75
PEG–camptothecin	Prothecan	Phase II	Various cancers	77

DACH, diaminocyclohexane; HPMA, *N*-(2-hydroxypropyl)methacrylamide; PEG, poly(ethyleneglycol).

Duncan *Nature Reviews Cancer* advance online publication;
published online 10 August 2006 | doi:10.1038/nrc1958

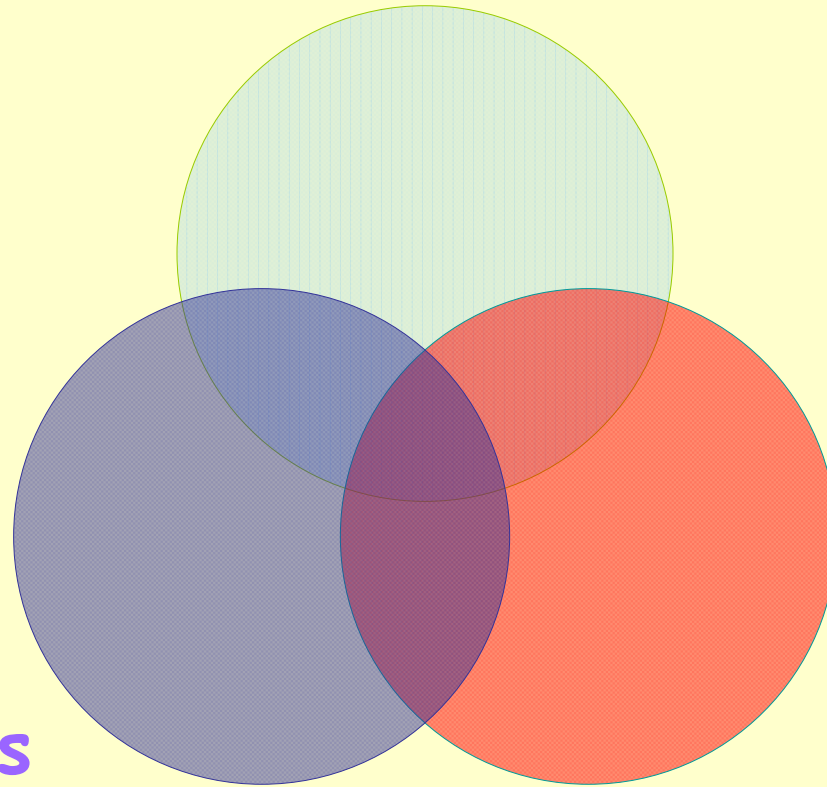
Summary of the different nanoparticles for drug delivery and imaging



Targeting and improving drug release at target

- Enhanced permeability and retention by large carriers of cancerous tissue
- Chemical specificity of interaction - **ligands and antibodies**
 - New types of targeting agents by rational design that uses structural knowledge of a docking
- Multi-target approaches dealing with target **cell heterogeneity**
- Methodologies for in-situ activation of **prodrugs** and smart agents
- Targeting to specific **intracellular targets** (compartment)
- Design of nanostructures with **stealth properties** (e.g. pegylation, adsorption of natural serum proteins)

delivery routes



nanocarriers

targeting