



DRUG DELIVERY SYSTEMS : CHALLENGES AND CLINICAL RELEVANCE

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- Introduction
- Drug Delivery : problems and challenges
- Nanotechnology-based DDS :
the case of IV administered nanoparticles
from research to clinical applications



Requirements (1) :

For systemic activity of an API molecule
after administration



it must be absorbed and enters the bloodstream / the
site of action
(except for IV route)



Requirements (2):

With a few exceptions, molecular dispersion of a drug is a prerequisite for its absorption across biological membranes



after administration the drug has to dissolve in the physiological fluid before crossing the biological barrier

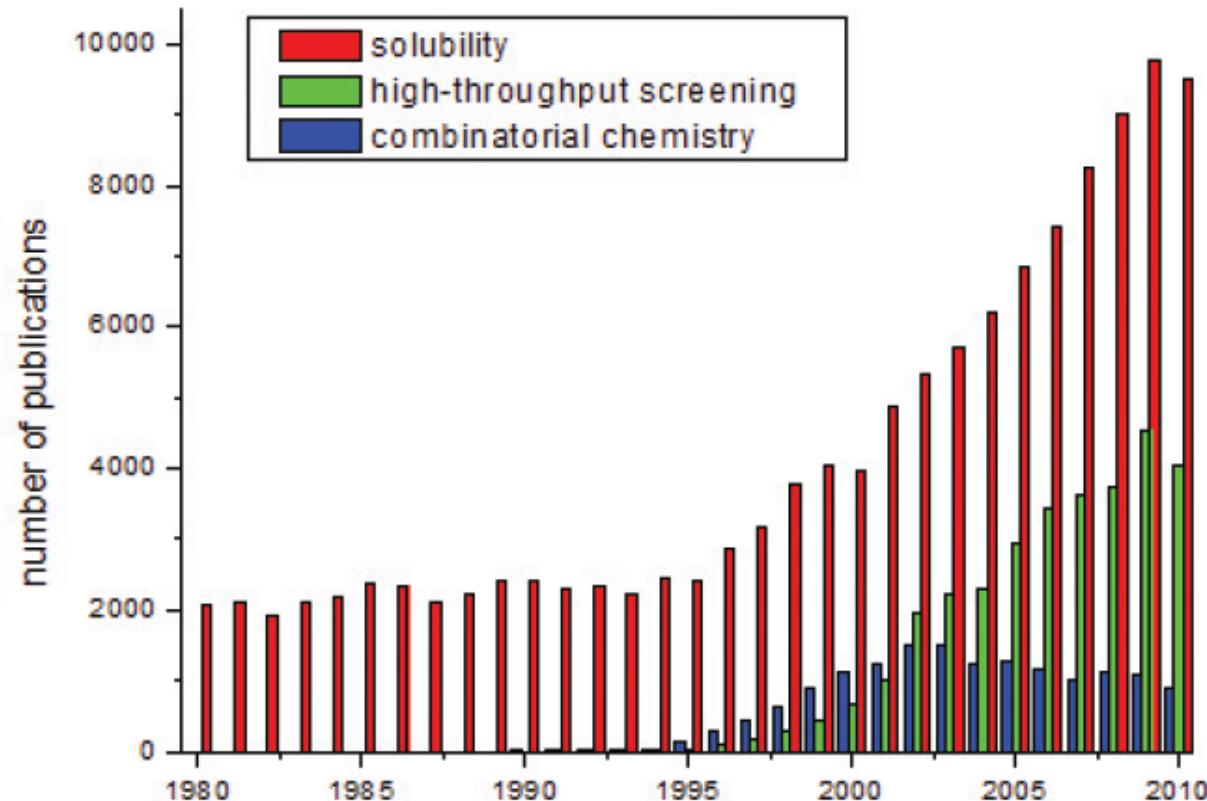
Needs to know :

- physiology of the administration site
- pharmaceutical form's behaviour
$$PF = API + excipients + process$$
- physicochemical parameters of API

Physicochemical parameters that influence bioavailability

- Solubility
- Dissolution rate
- pKa
- Partition coefficient
- Solid state
- Size in case of solids
- Stability

Solubility = Cs



.... don't forget the DOSE

Strategies and challenges:

The case of poorly soluble drugs

Use of excipients :

but ... stability, compatibility, toxicity, cost, ...

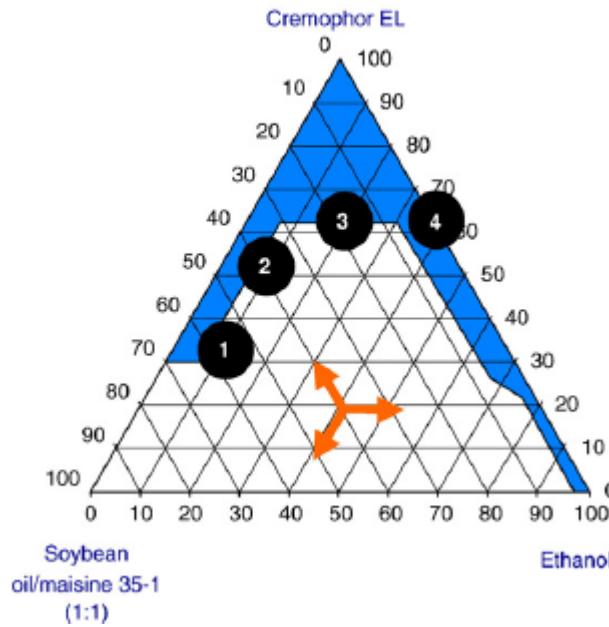
Route of administration,...

Conventional approaches :

- pH adjustment : mainly parenteral administration
- salts
- cosolvents
- surfactants
- cyclodextrins
- lipid-based DDS (Emulsions, microemulsions, SMEDDS, SNEDDS)
- solid state (polymer matrix, nanosuspensions)

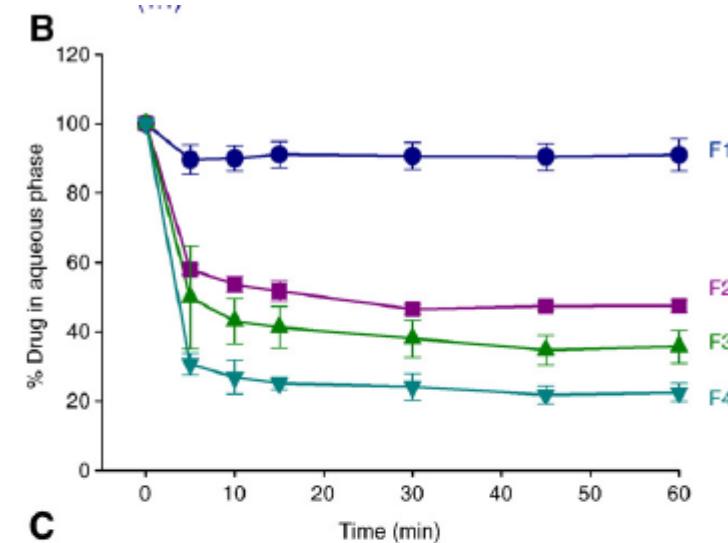
SEDDS : Formulation/Solubilization/Bioavailability

A

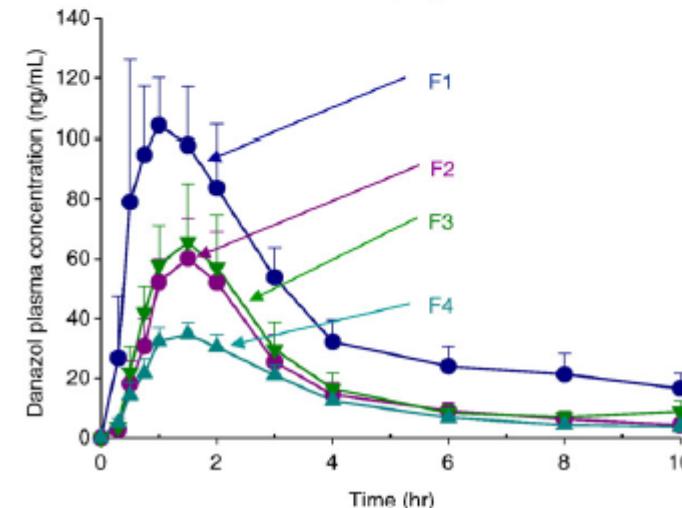


- F1: 60% w/w soybean oil/Maisine 1:1; 30% Cremophor EL, 10% ethanol
- F2: 37.5% w/w soybean oil/Maisine 1:1; 55%Cremophor EL, 7.5% ethanol
- F3: 18% w/w soybean oil/Maisine 1:1; 64% Cremophor EL, 18% ethanol
- F4: 65% Cremophor EL, 35% ethanol

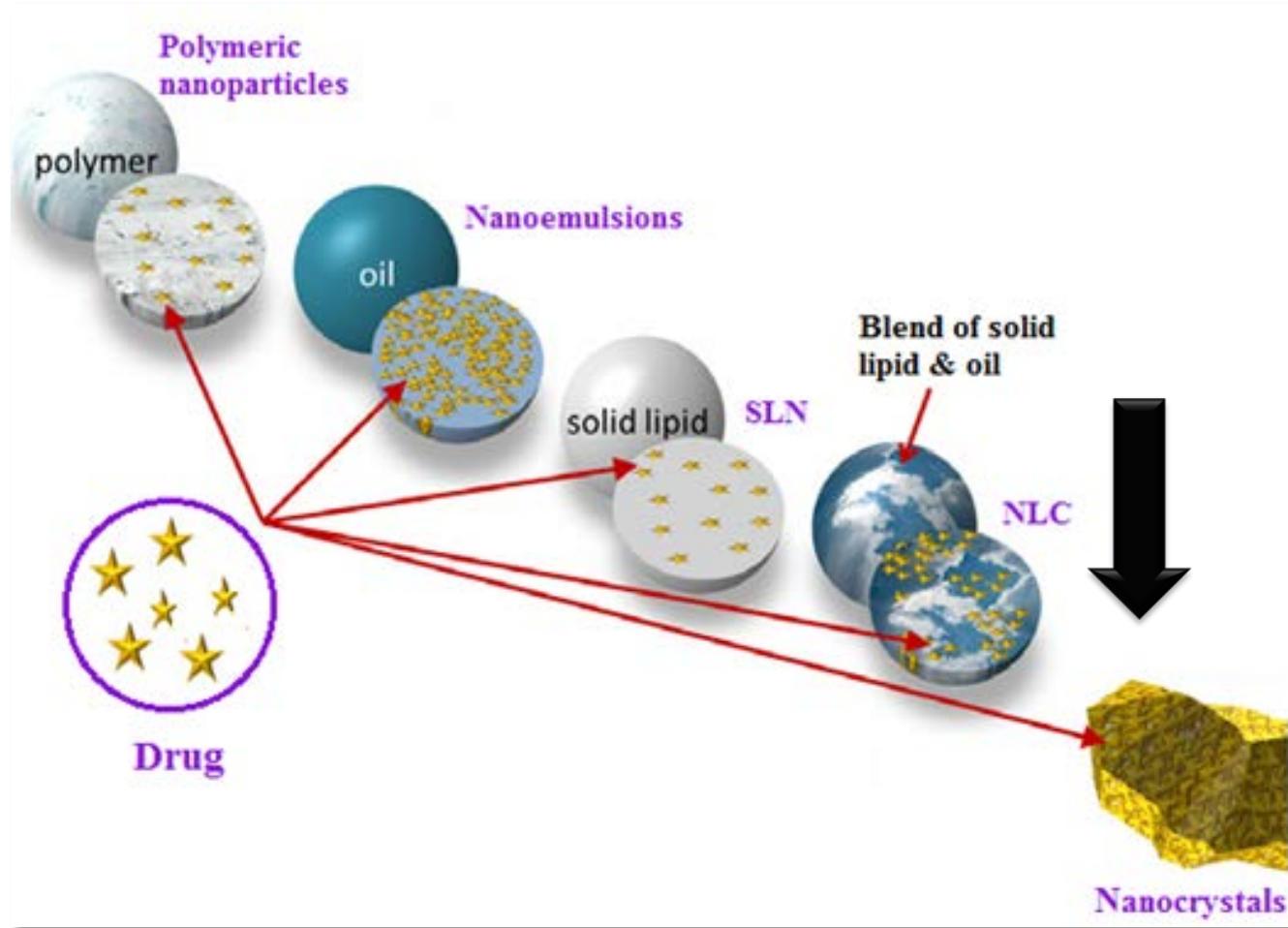
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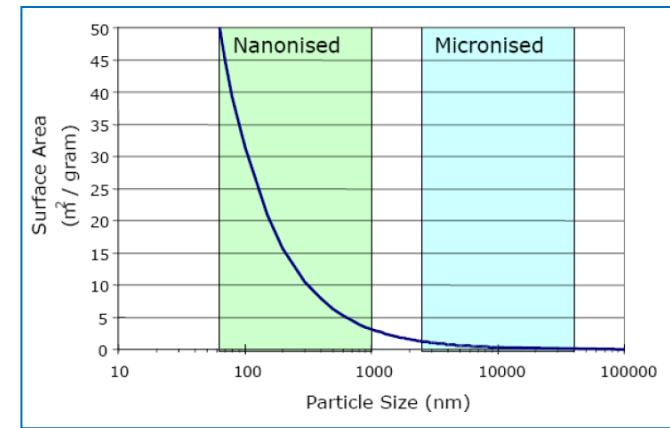
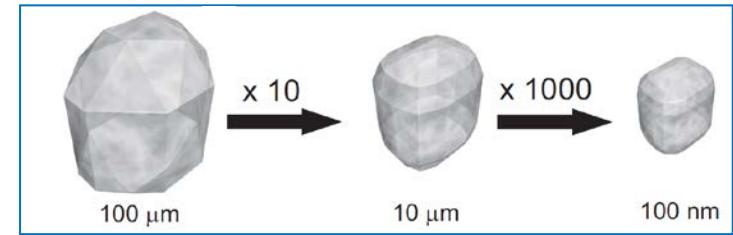
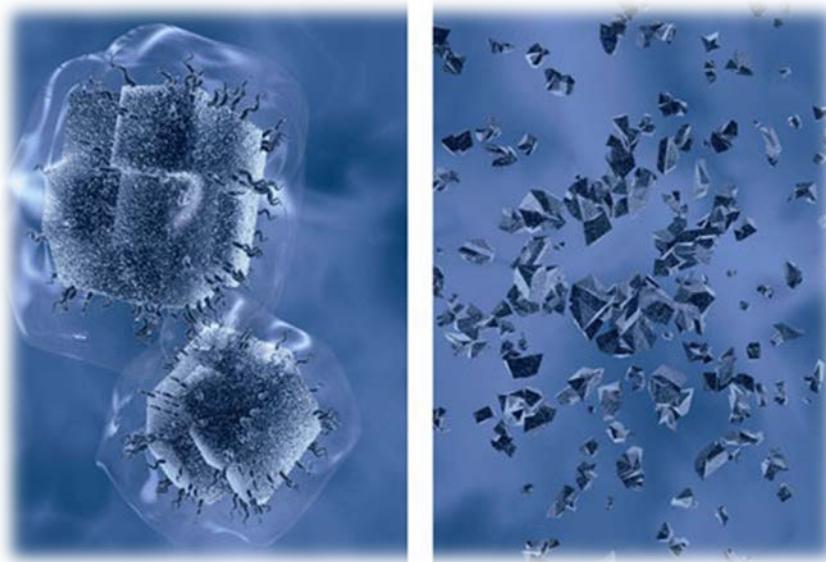
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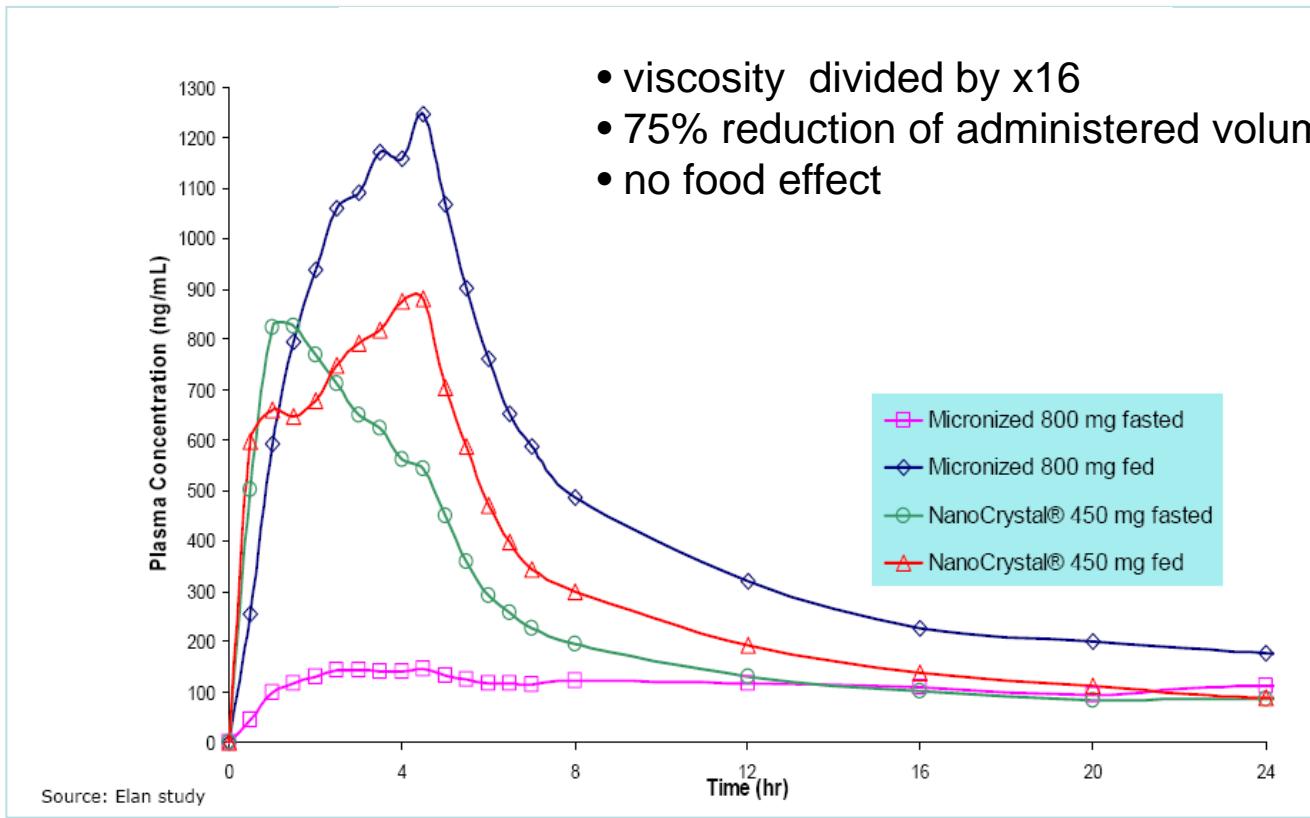
... and nanoparticles as:



Nanosuspensions:



Megace® ES (megestrol acetate, oral suspension)



Focus on

Nanotechnology-based DDS The case of intravenous administration

Instead of controlled-release systems

Nancapsules
Nanospheres
Polymersomes
Dendrimers

SLN
Liposomes
SLN, NLC

HSA-Drug NPs
VLP

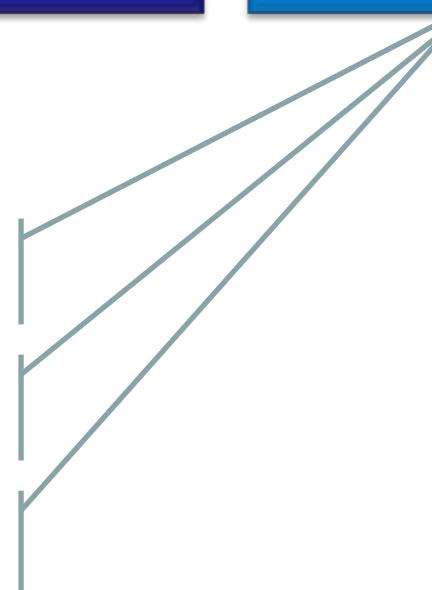
Polymers

lipids

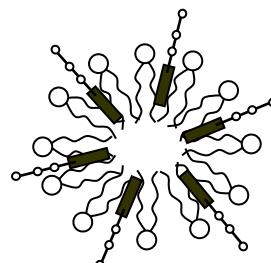
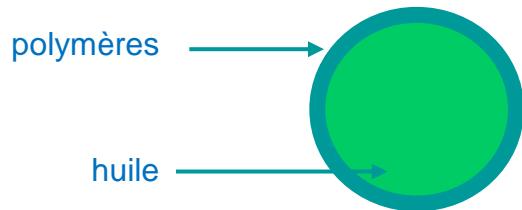
Proteins

inorganic

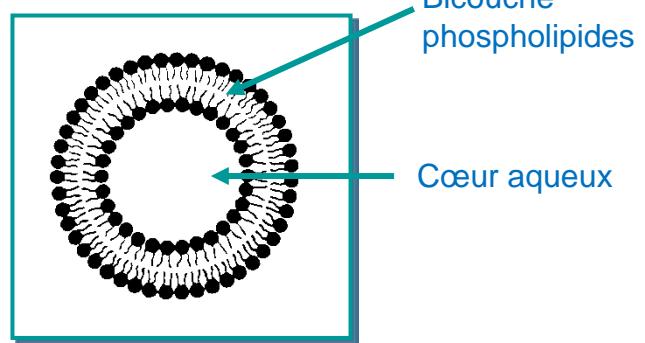
Iron oxyde
gold
silica



Nanoparticules

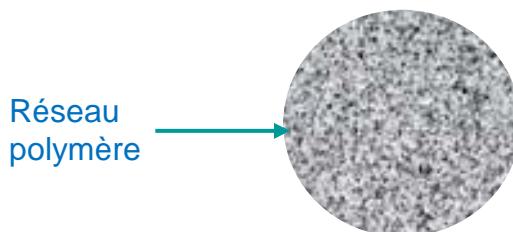


Micelle



Liposome

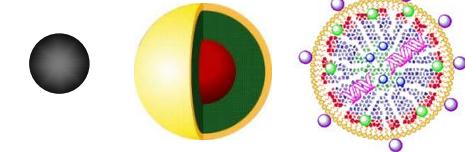
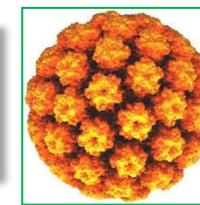
Micro- or nanocapsules



Micro- or nanosphères



protéines

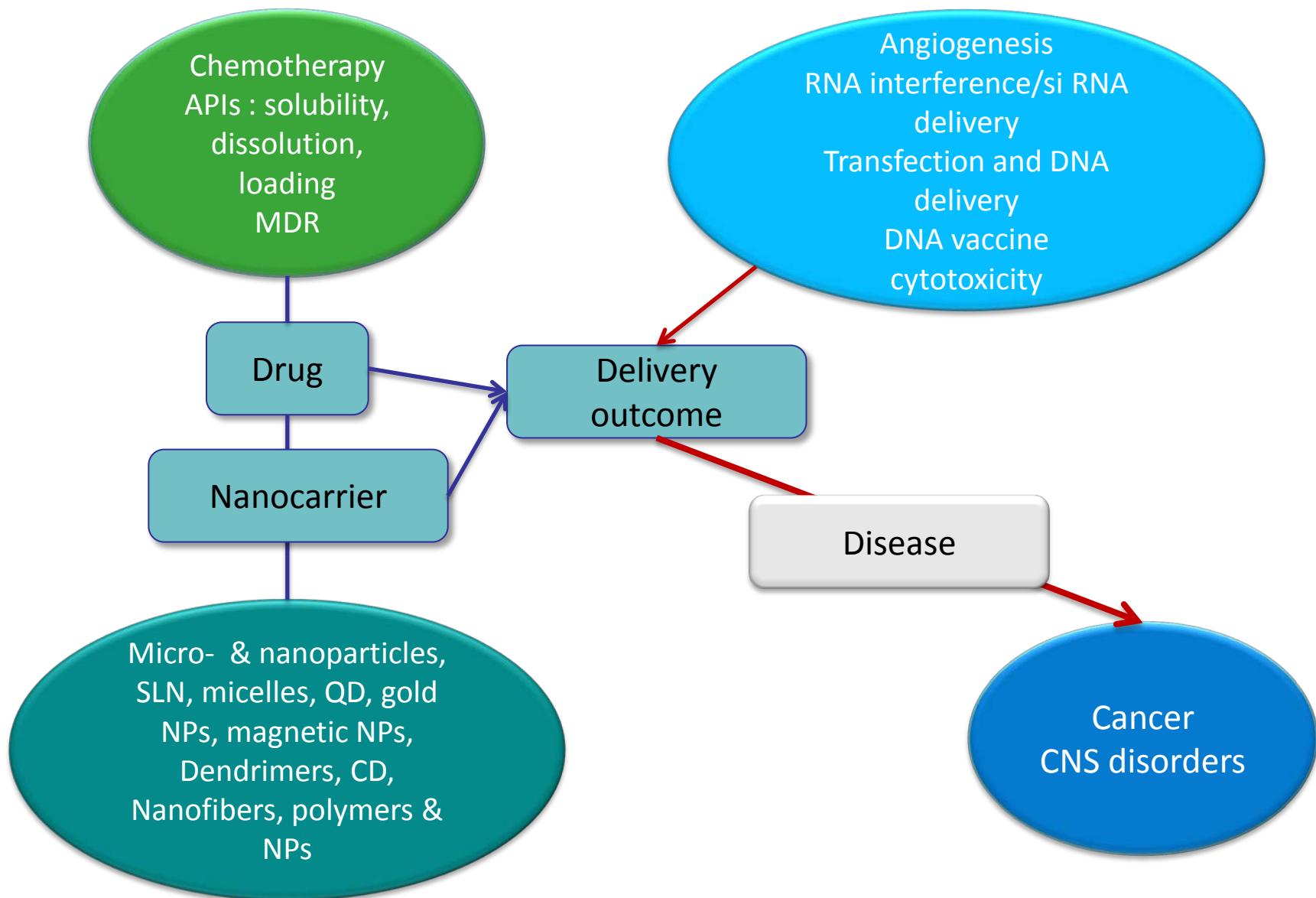


inorganiques

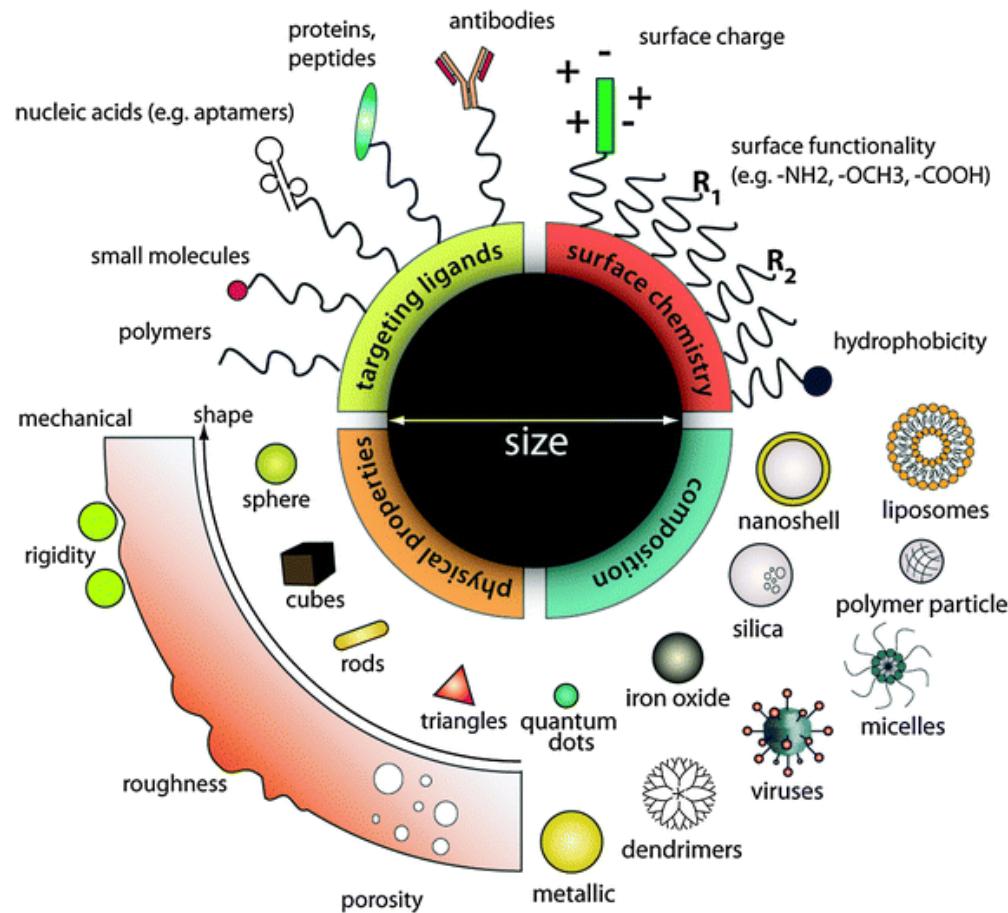
Nanostructuré = nanomatériaux



Solides : monolithes, divisés, 2D, 3D



Towards multifunctional nanoparticles (i.e. Theranostic)



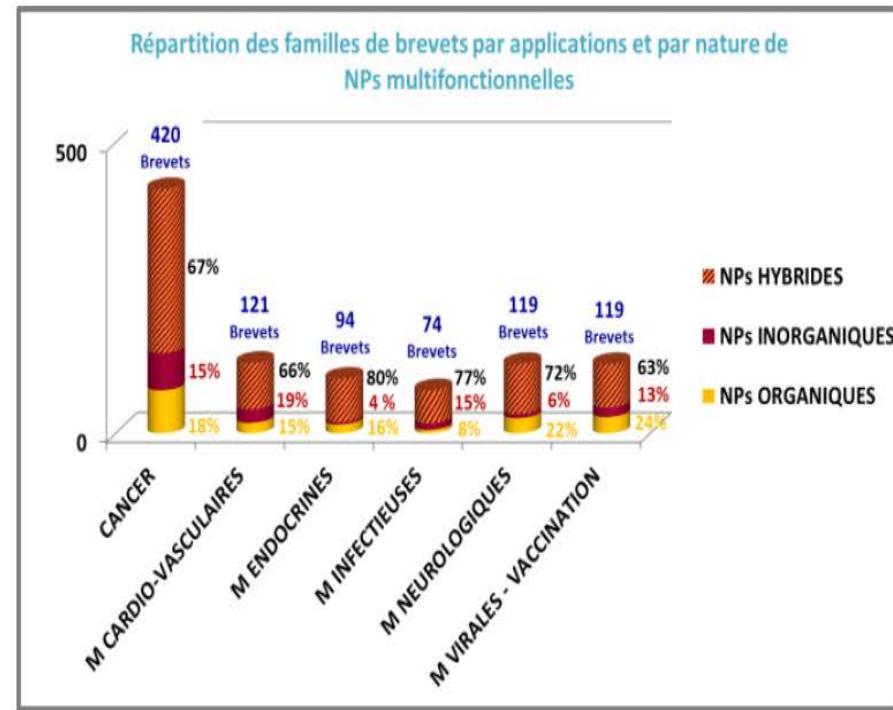
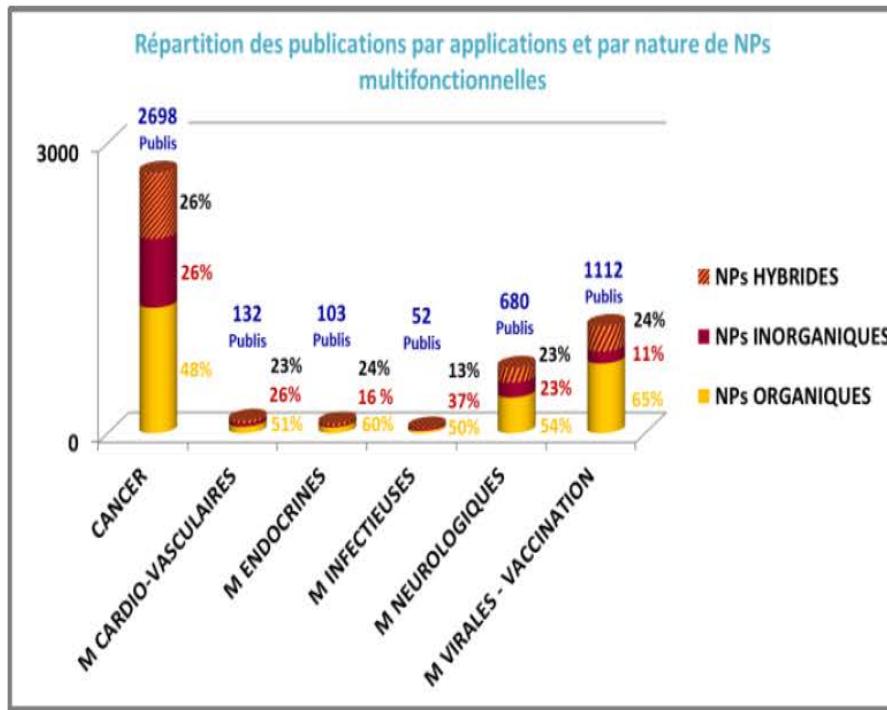
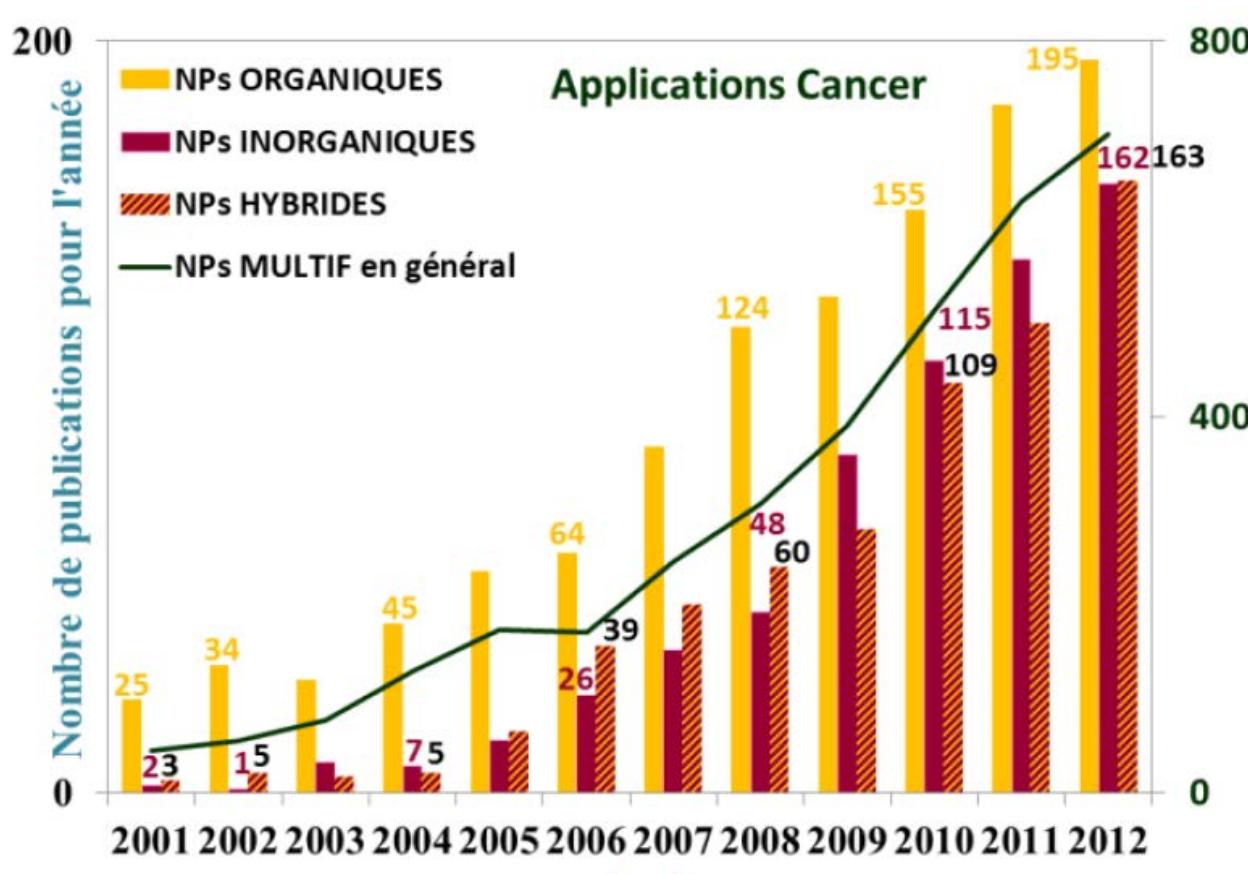
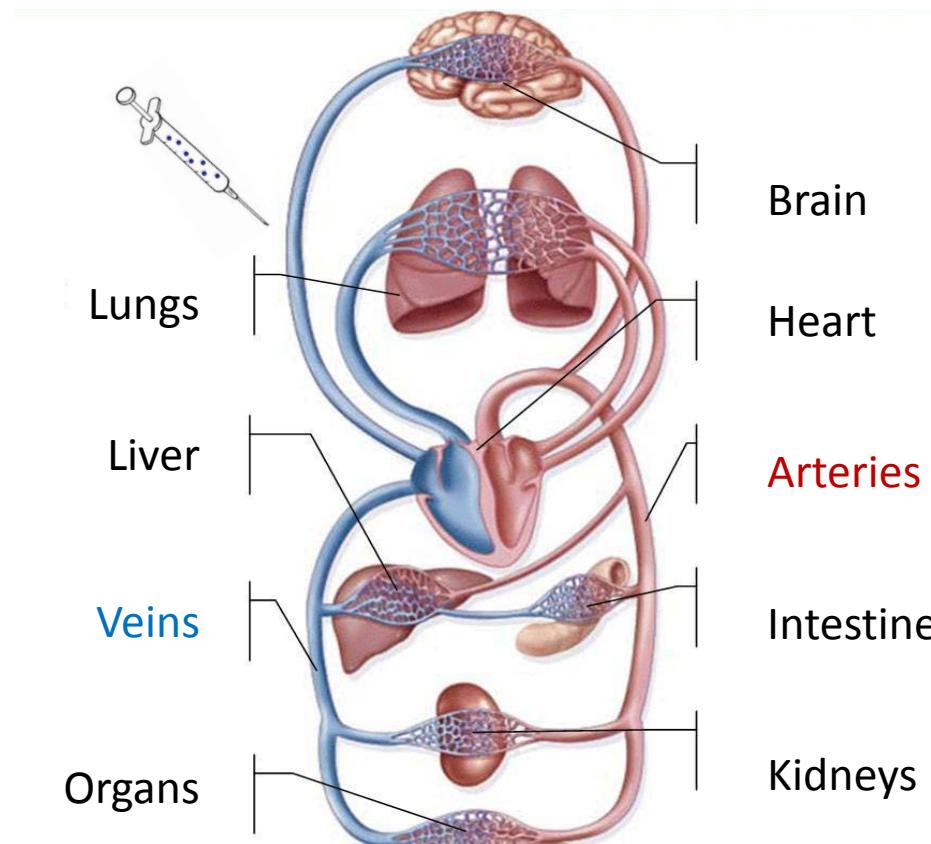


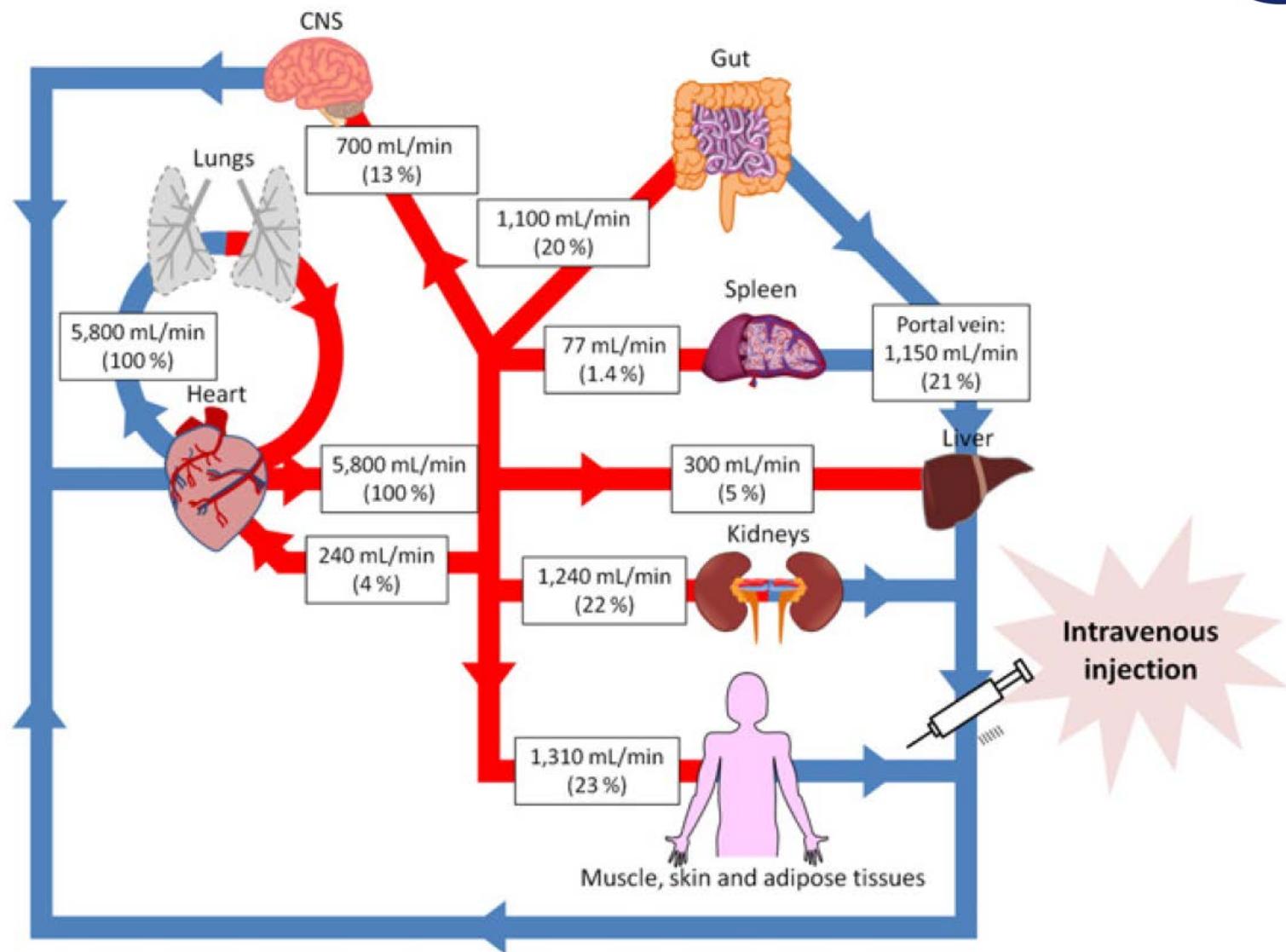
Figure 16: Proportions de NPs multifonctionnelles organiques, inorganiques ou hybrides pour chaque domaine d'applications envisagé (M pour maladies)

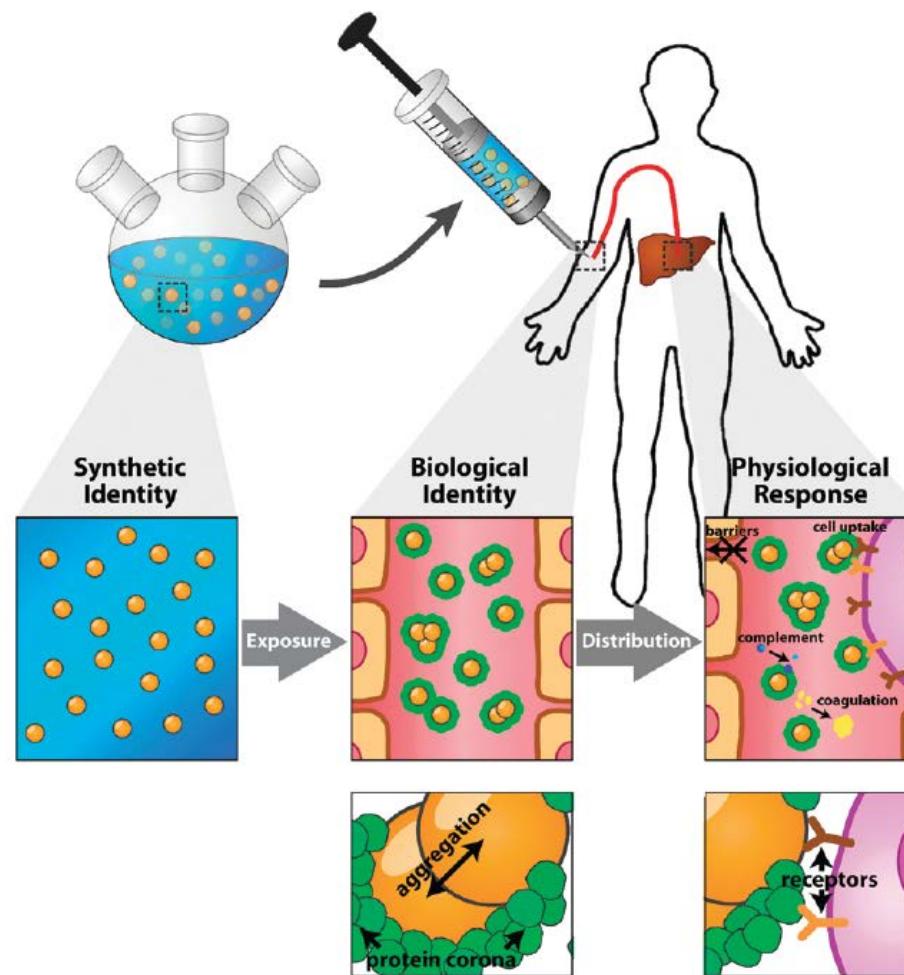


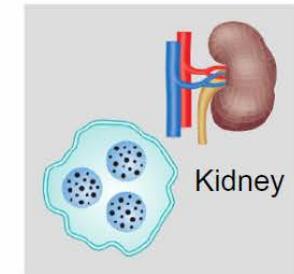
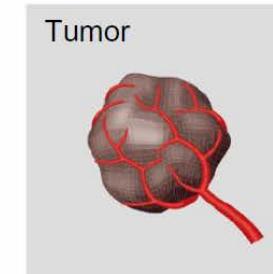
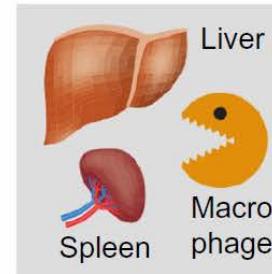
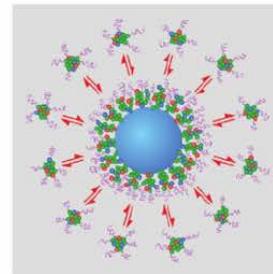
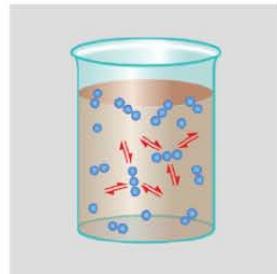
Source : OMNT Etude sur NPs multifonctionnelles – octobre 2013

Nanotechnology-based DDS (NPs) and i.v. administration : *in vivo* behavior and physiological barriers









A
Agglomeration
Deagglomeration
Precipitation



B
Protein
coating



C
Elimination
by MPS



D
Accumulation
at target site/
cellular uptake



E
Biodegradation
Elimination

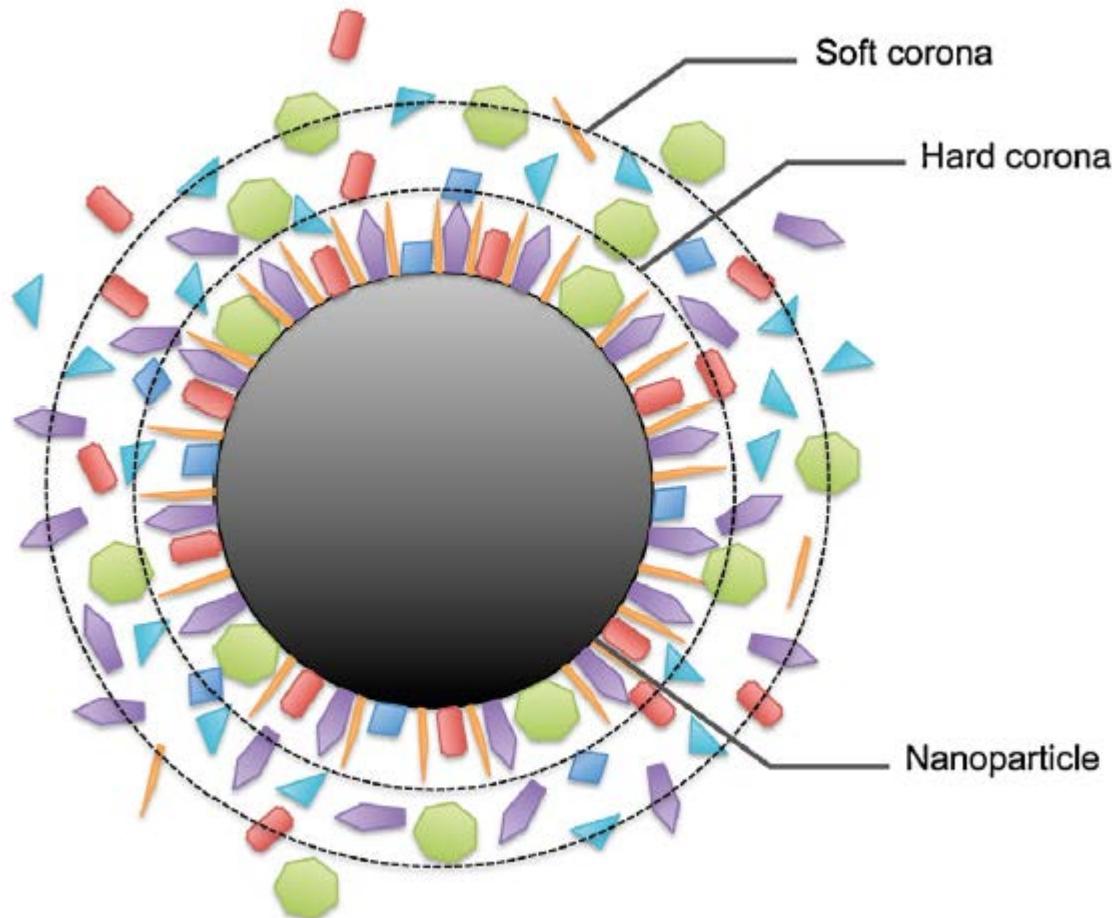
Interactions of NPs with blood components

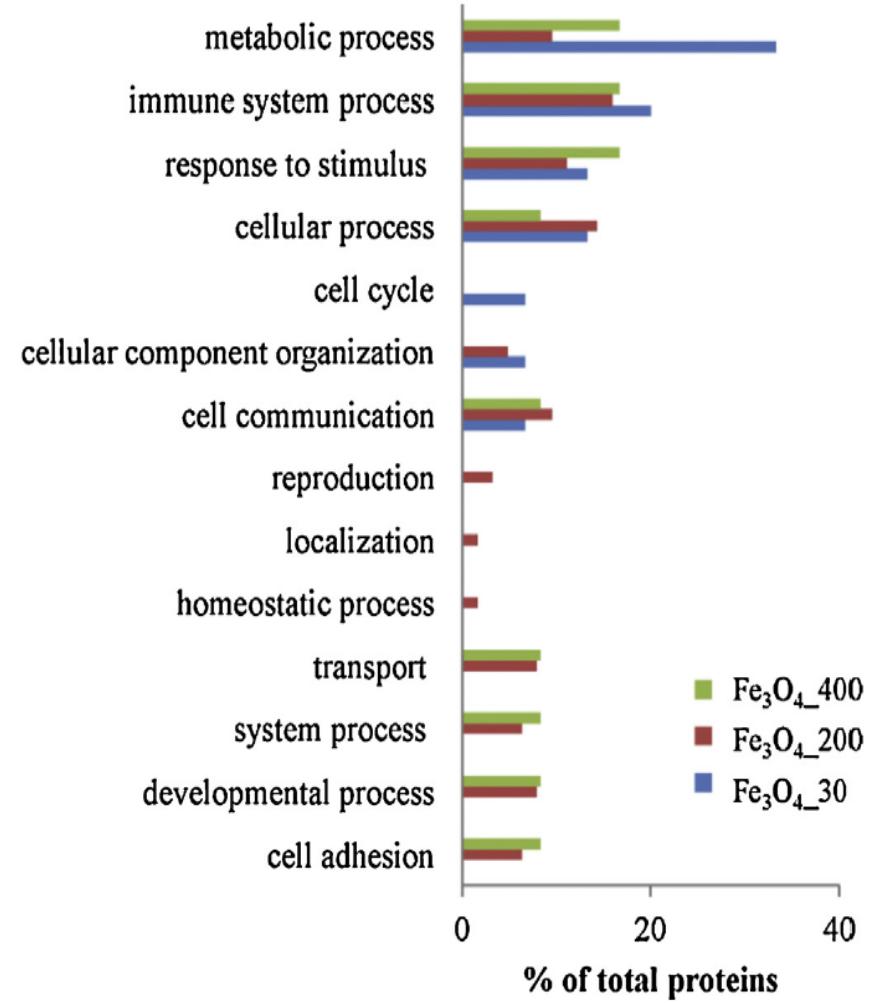
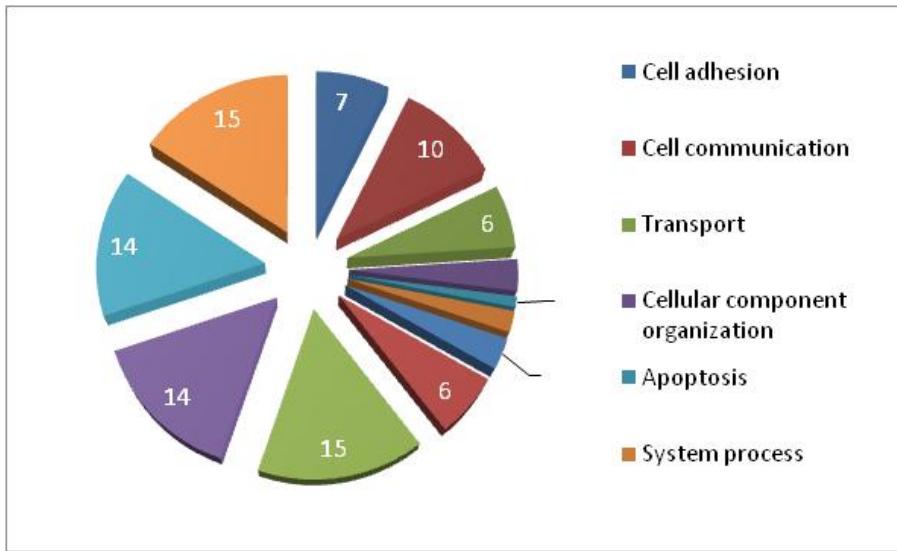
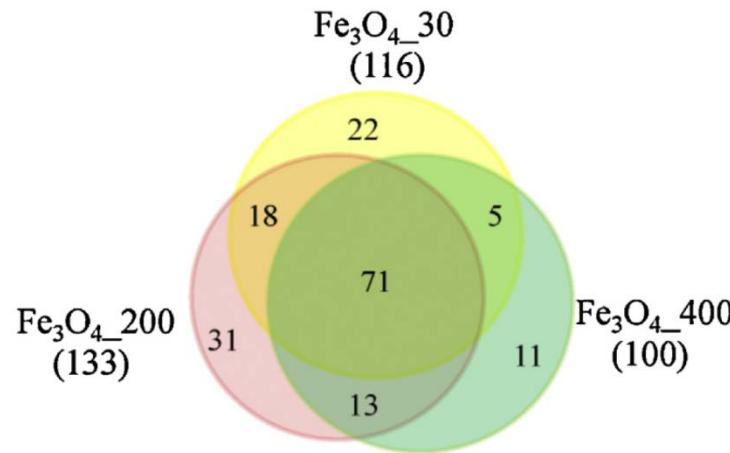
Components	Changes	Implications
Nanoparticle	<ul style="list-style-type: none">• Size• Shape• Charge• Aggregation	<ul style="list-style-type: none">• Toxicity• Immunological recognition• Molecular targeting• Biodistribution• Intracellular uptake• Drug release
Proteins	<ul style="list-style-type: none">• Structural modifications• Aggregation → Loss of functional activity	<p>→ Biocompatibility and efficacy</p>

Physiological barriers include ... physical barriers:

- Diffusion and Brownian **motion in complex tissues** including the (cell cytoplasm and extracellular space): **limitation of the translocation** of particles
- Particle **aggregation and flocculation**: *in vivo* adversely affecting particle behavior
- Particle **flow and shear forces** and interactions with target (and non-target) tissues and tumor receptors
- Particles and the enhanced permeability and retention (EPR) effect: size, shape, jamming and kinetics
- Intrinsically heterogeneous **distribution** of both free drug and **nanoparticles** in tumor

Interactions of NPs with blood components

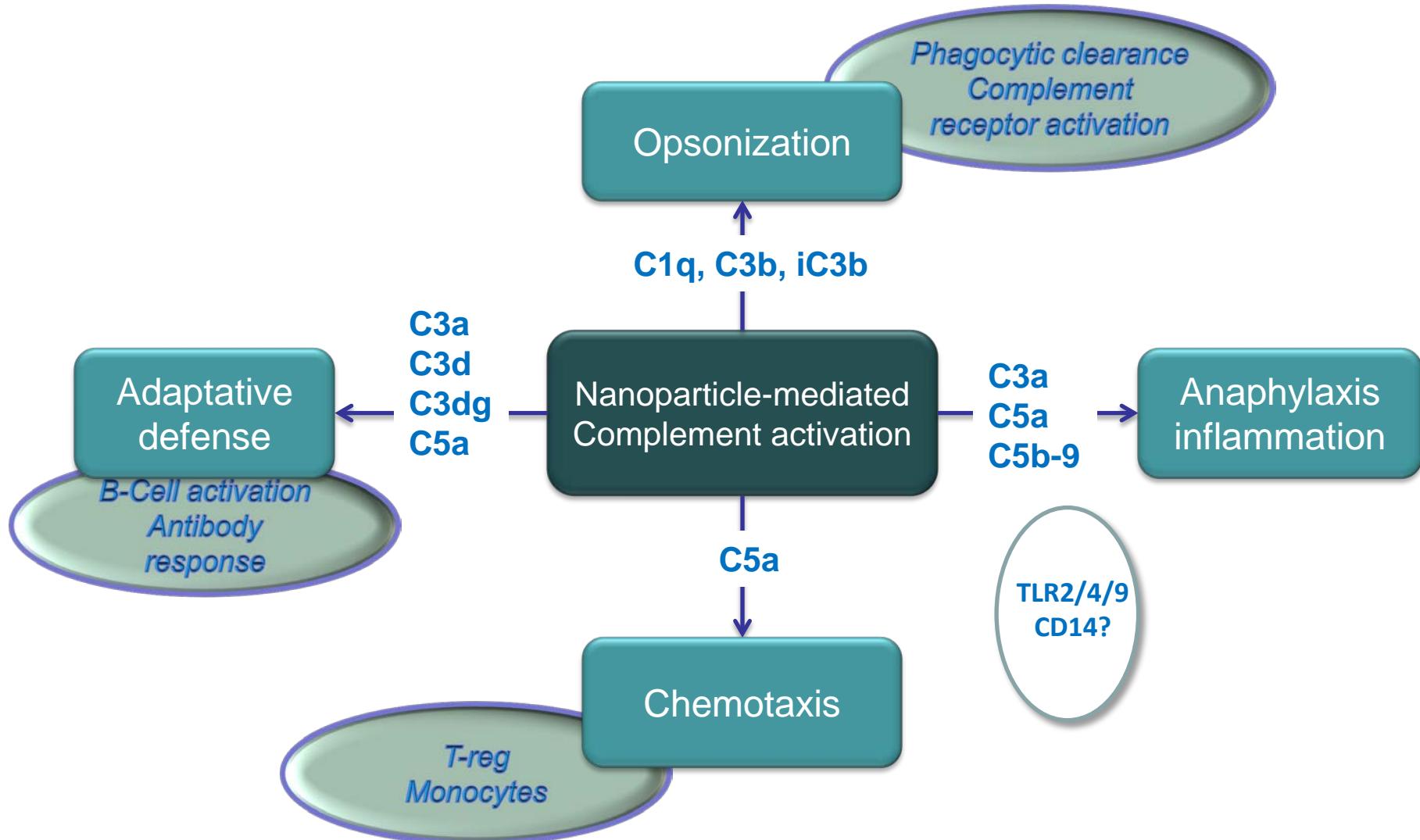




Nanoparticle-mediated complement activation

The immune system :

- protects the organism from attacks by complex mechanisms
- able to recognize almost anything that is ‘foreign’ to the host
- recognize **synthetic as well as natural materials**, all of which have distinct molecular surface features.
- ***the complement system plays a major role***

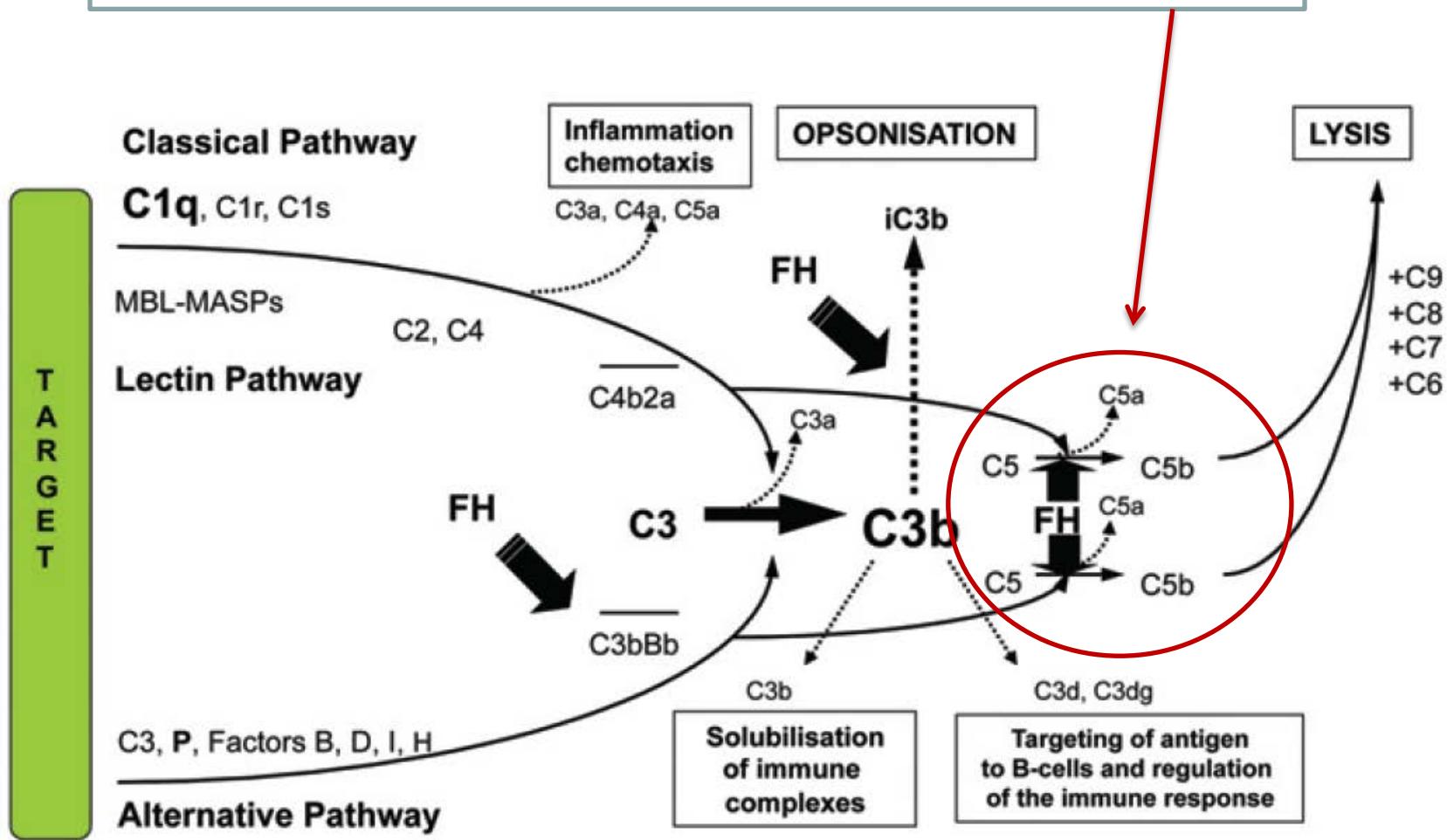


Mechanism of opsonization:

- complement proteins binding to foreign particles
- triggering the formation of a series of proteolytic enzymes
- Activation of the C3 protein (2% of total blood plasma protein)
- The activated C3 undergoes a transesterification reaction with hydroxyl, amine or thiol groups on the particle surface **to form a covalent bond.**
- Once the particle is coated with many C3 molecules ('**opsonized**'), adhesion to phagocytic cells that **have C3 receptors** on their surface
- subsequently **ingestion** of foreign particles

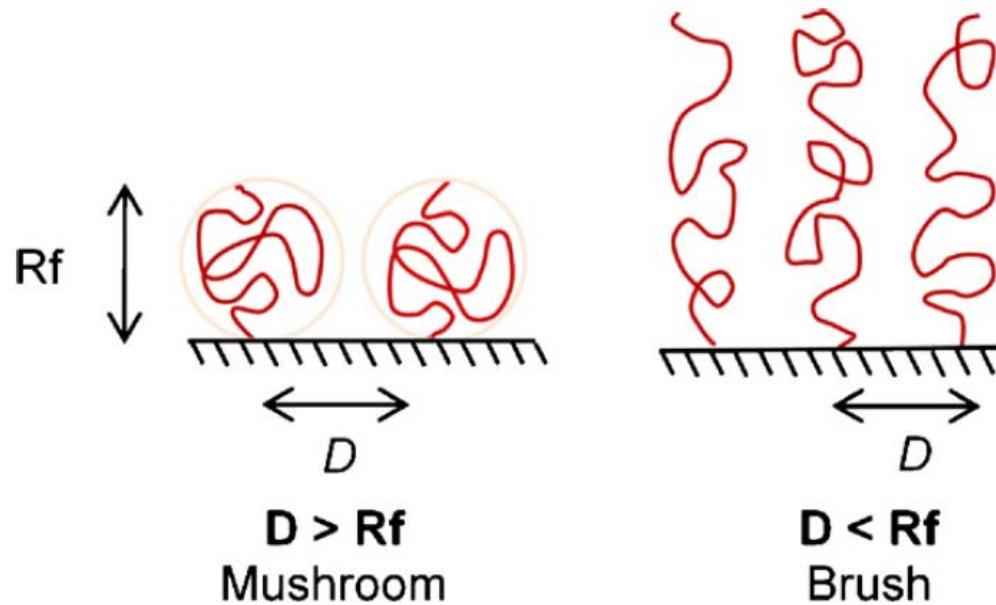
Consequences : NPs may be taken up by phagocytic cells before they reach their target, and/or may be inflammatory!

C5 forms a 'membrane attack complex' to burst foreign materials that have a lipid bilayer membrane (i.e. liposomes)

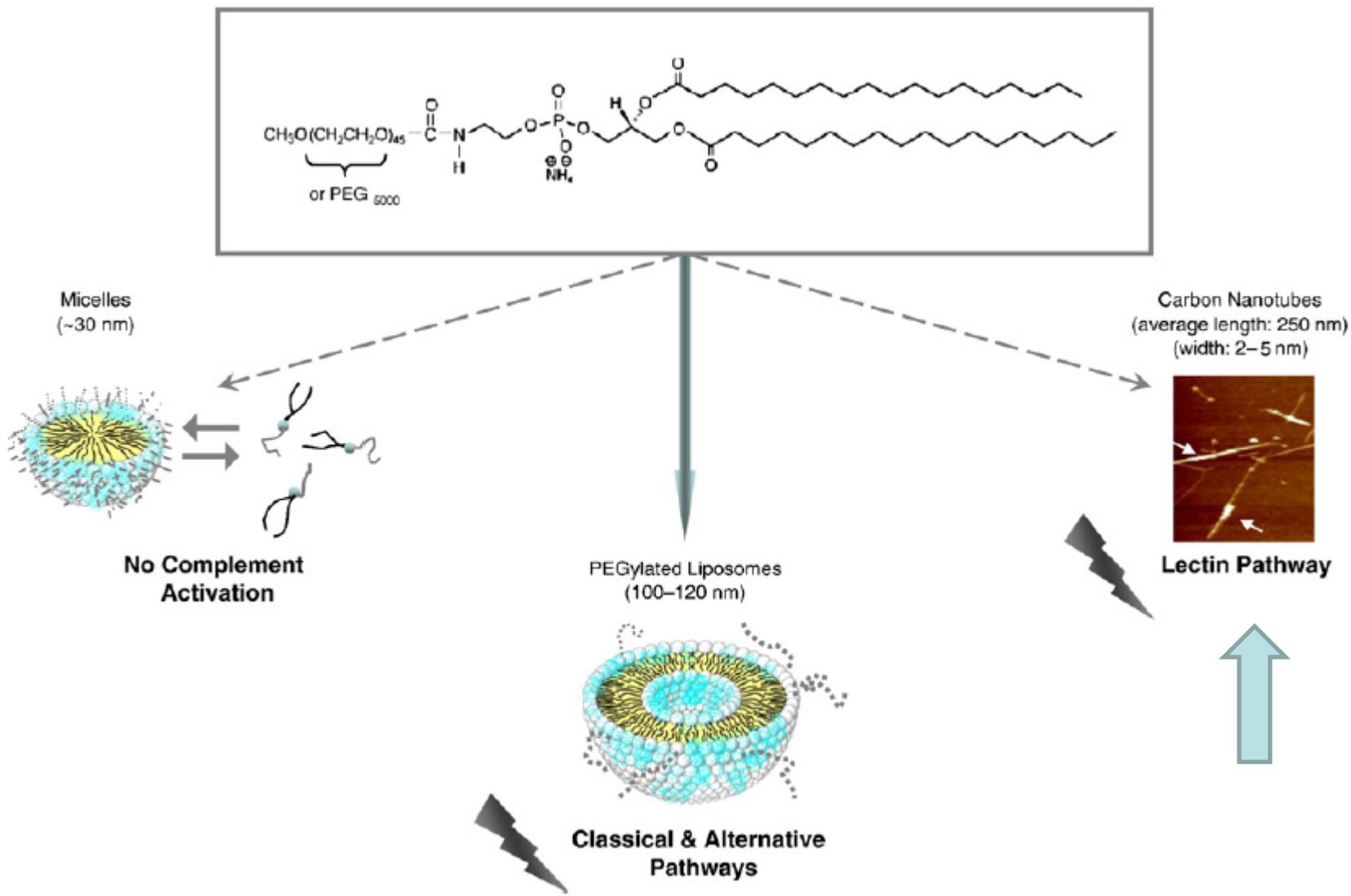


What about stealthiness ?

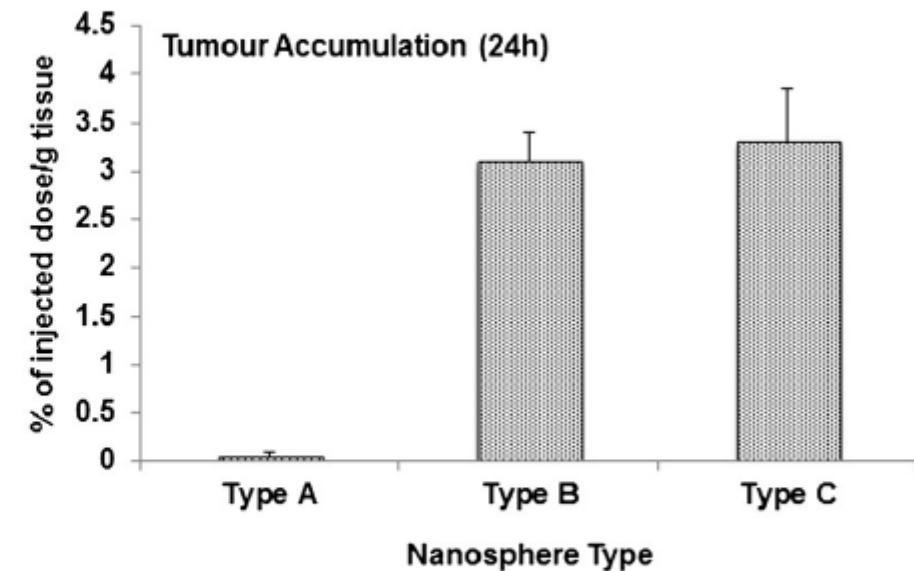
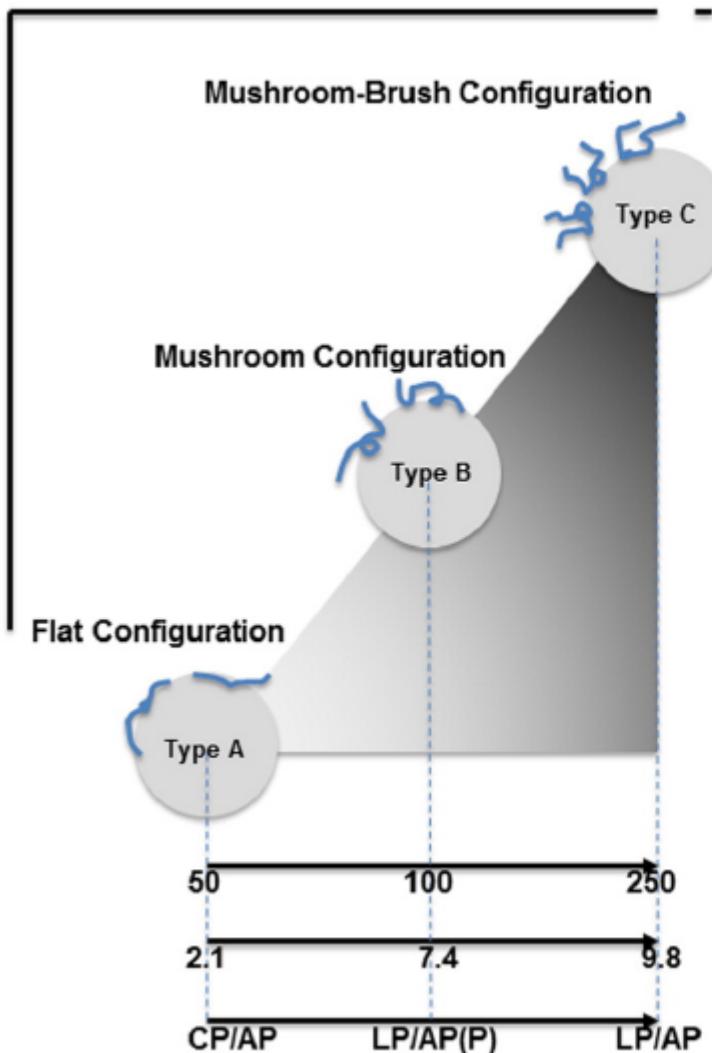
Representation of different PEG conformations, formed through their incorporation PEG onto surfaces at different densities.

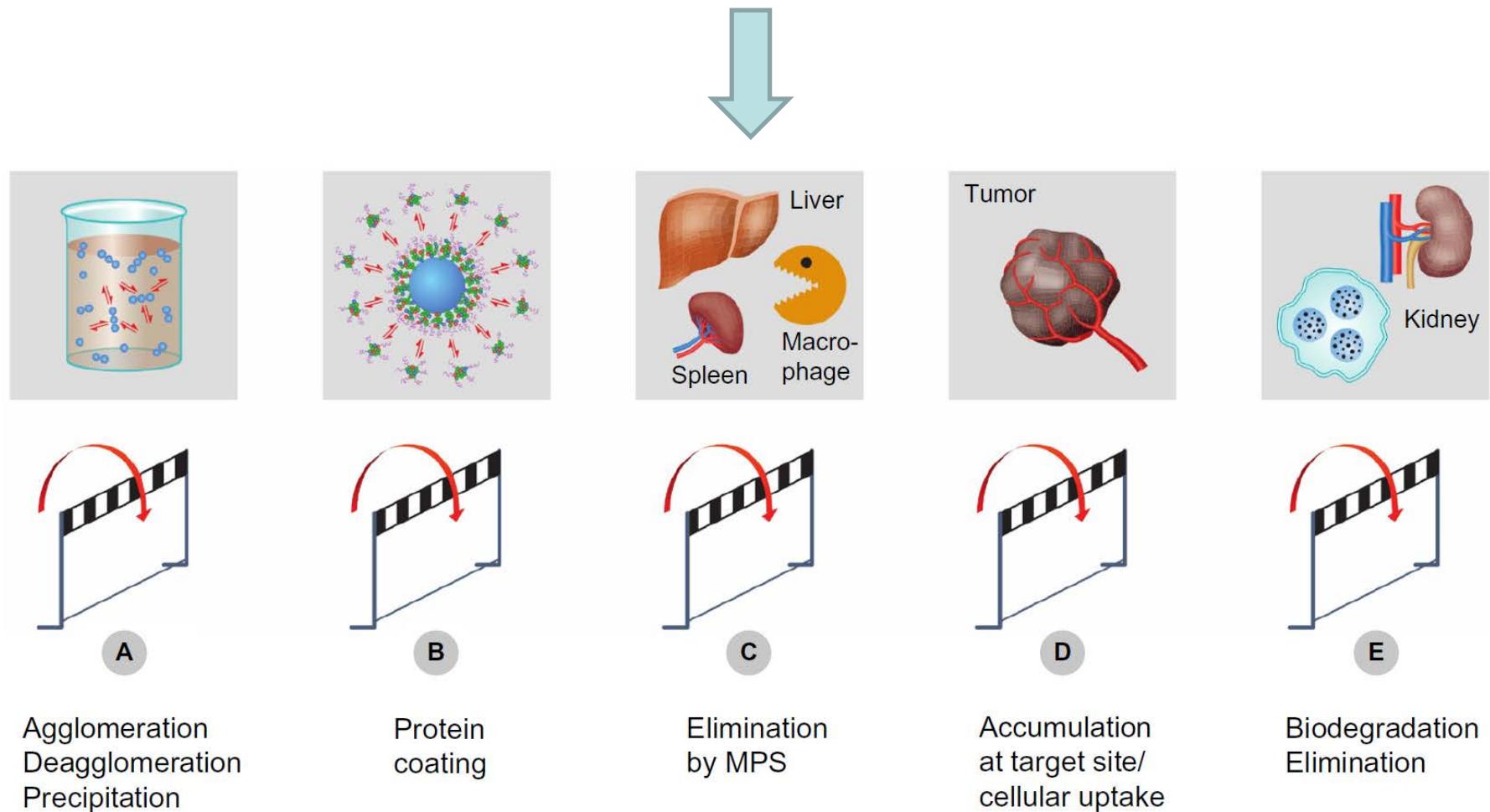


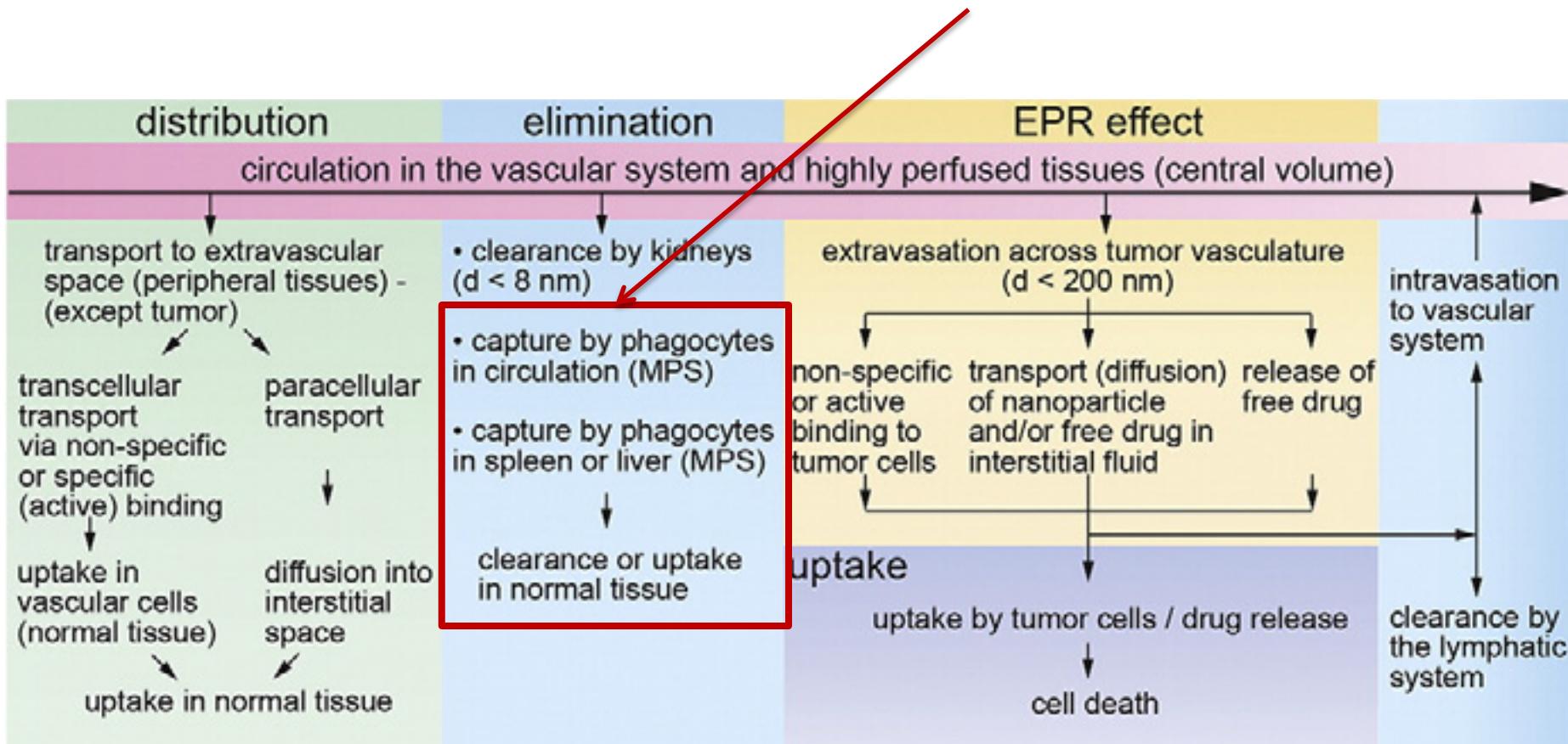
If $D >$ Flory diameter of the PEG ($D > R_f$) collapse into a **mushroom**
 If $D < R_f$, the PEG chains : extended from the surface to form a **brush-like conformation**



Projected PEO Chain Configuration





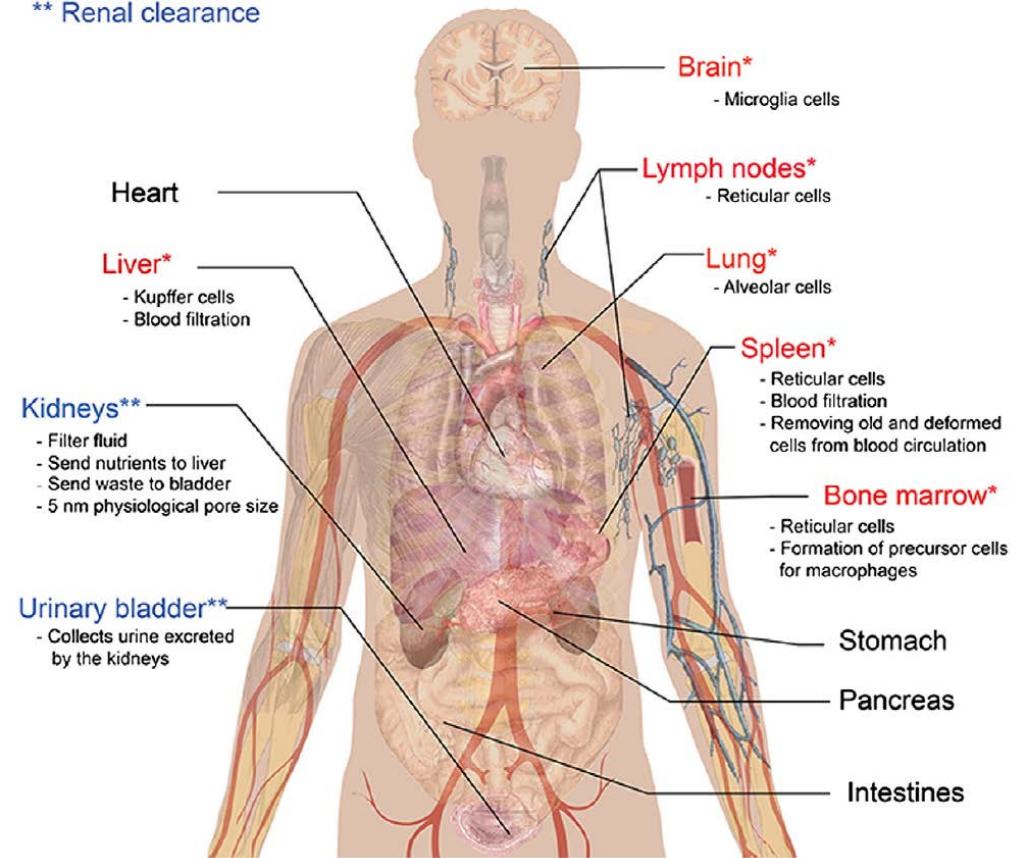


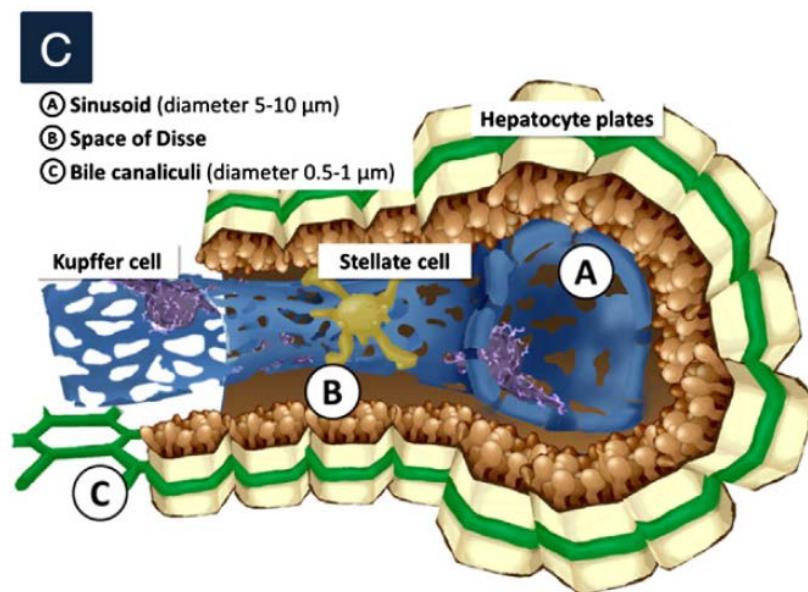
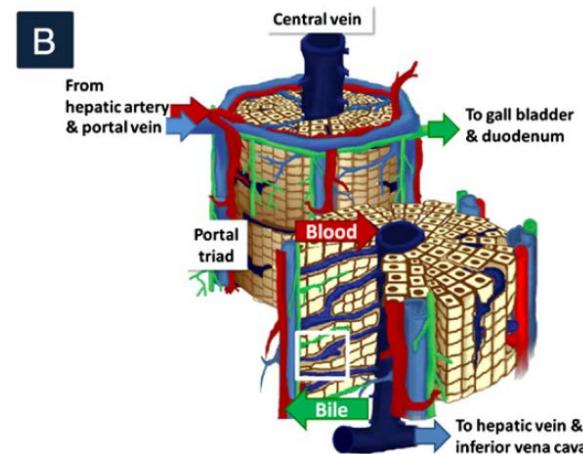
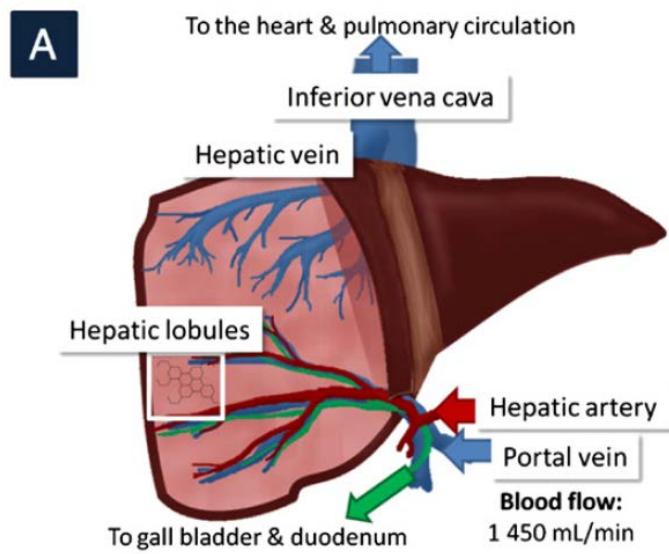
The mononuclear phagocyte system (MPS):

- Phagocytes, monocytes, and dendritic cells in the MPS participate in the response to inflammation and infection.
- Phagocytes are responsible for removing pathogens and foreign bodies such as nanoparticles from circulation
- Opsonins that bind to nanoparticles initiate uptake and removal from circulation by phagocytes.

* Mononuclear Phagocyte System (MPS)

** Renal clearance

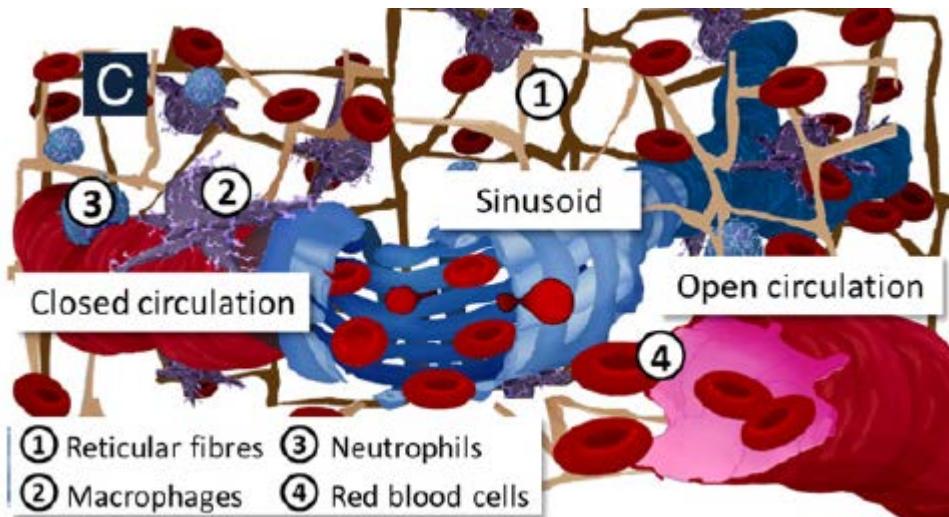
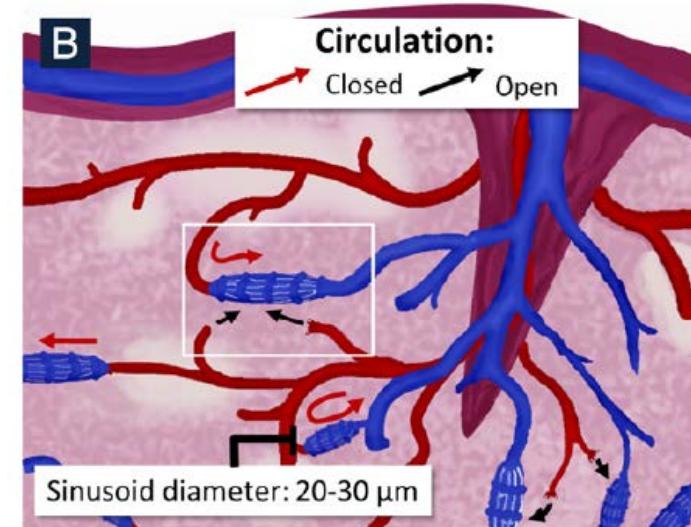
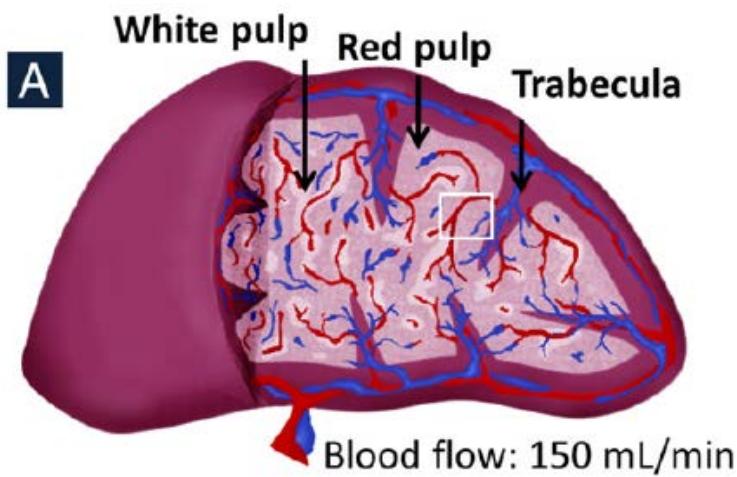




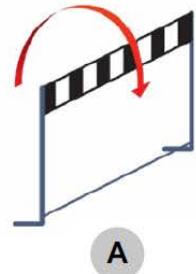
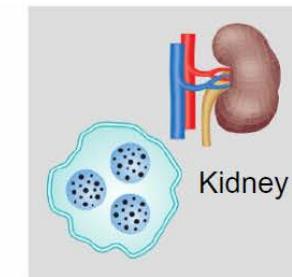
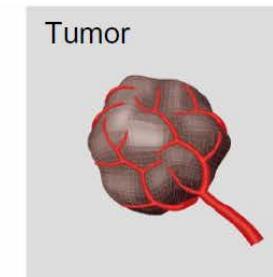
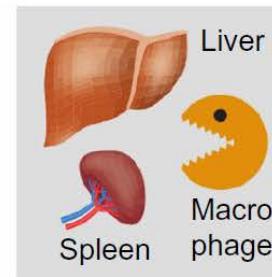
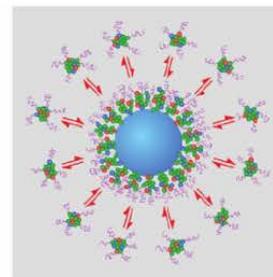
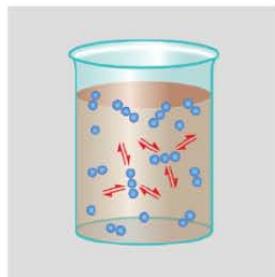
Kupffer cells :

- phagocytic activity of the liver
- 80 to 90% of the total body macrophage population

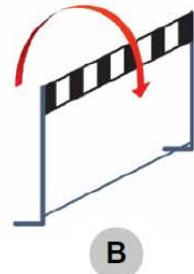
Sinusoids : the size of the fenestrations (100 to 150 nm depending on the animal species)



Reticular fibres confer a highly-tortuous architecture to the red pulp, and blood components must squeeze through the 200-nm wide fenestration of the sinusoids



A
Agglomeration
Deagglomeration
Precipitation



B
Protein
coating



C
Elimination
by MPS

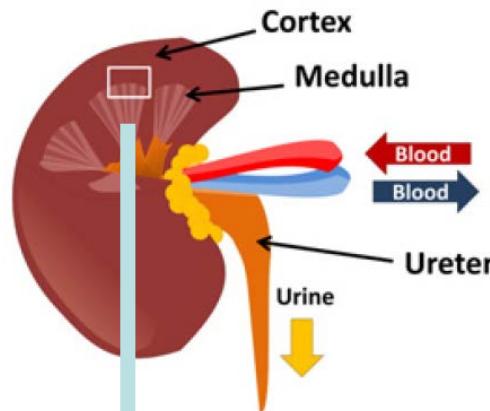


D
Accumulation
at target site/
cellular uptake

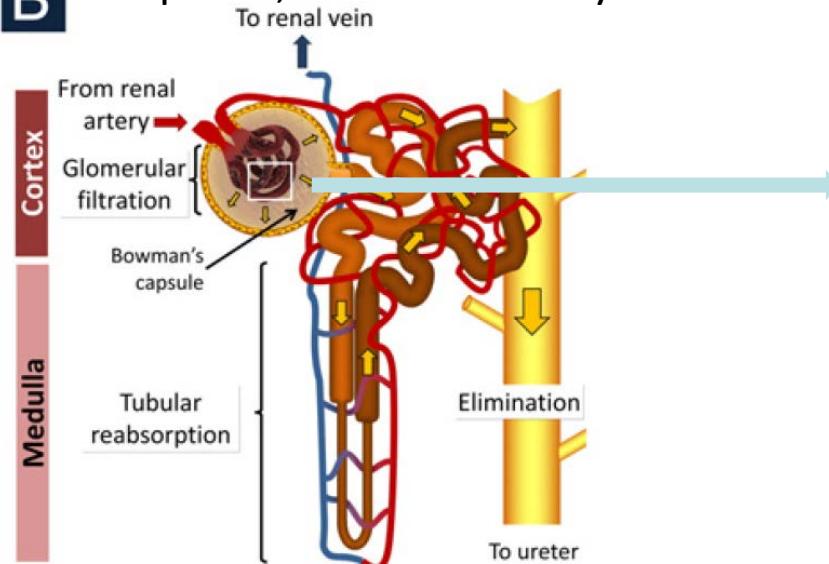


E
Biodegradation
Elimination

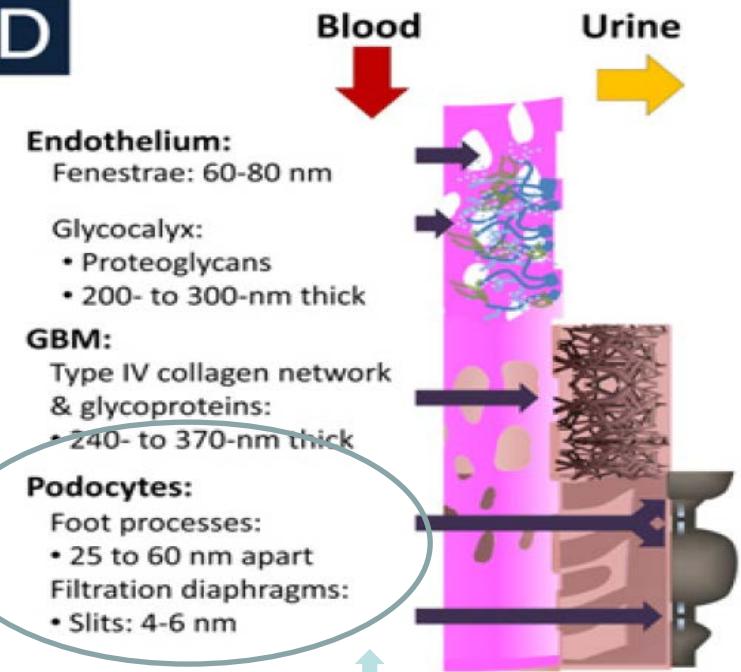
A Kidney



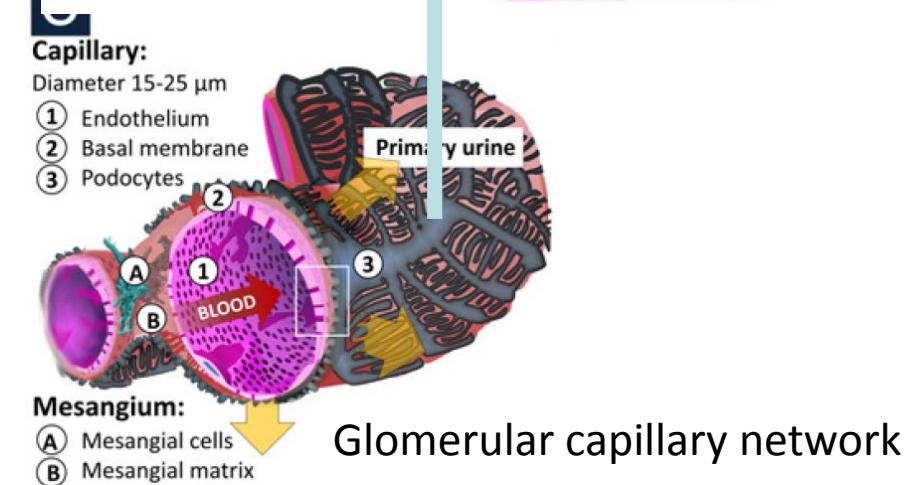
B Nephron, the basic kidney functional unit



D

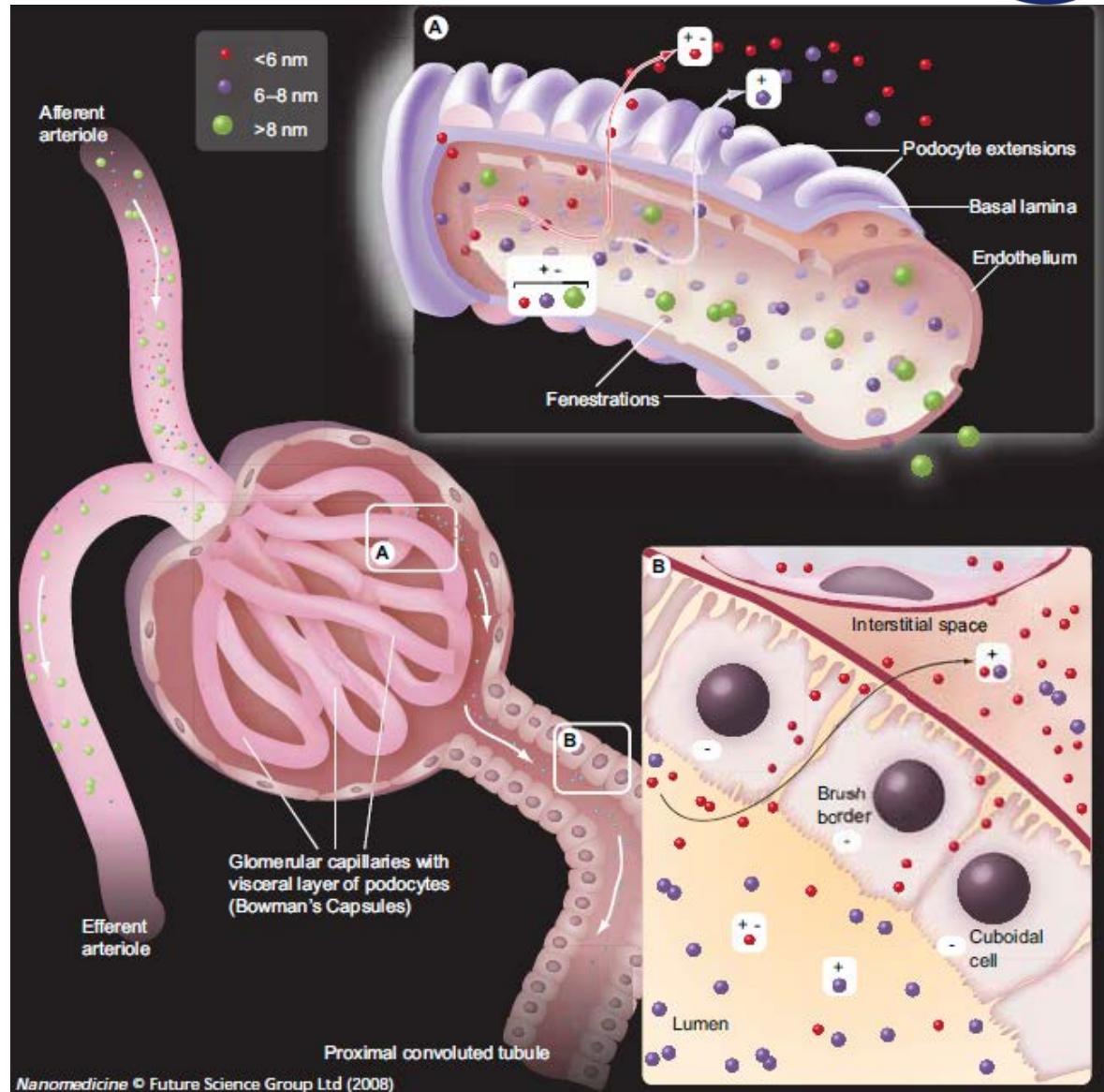


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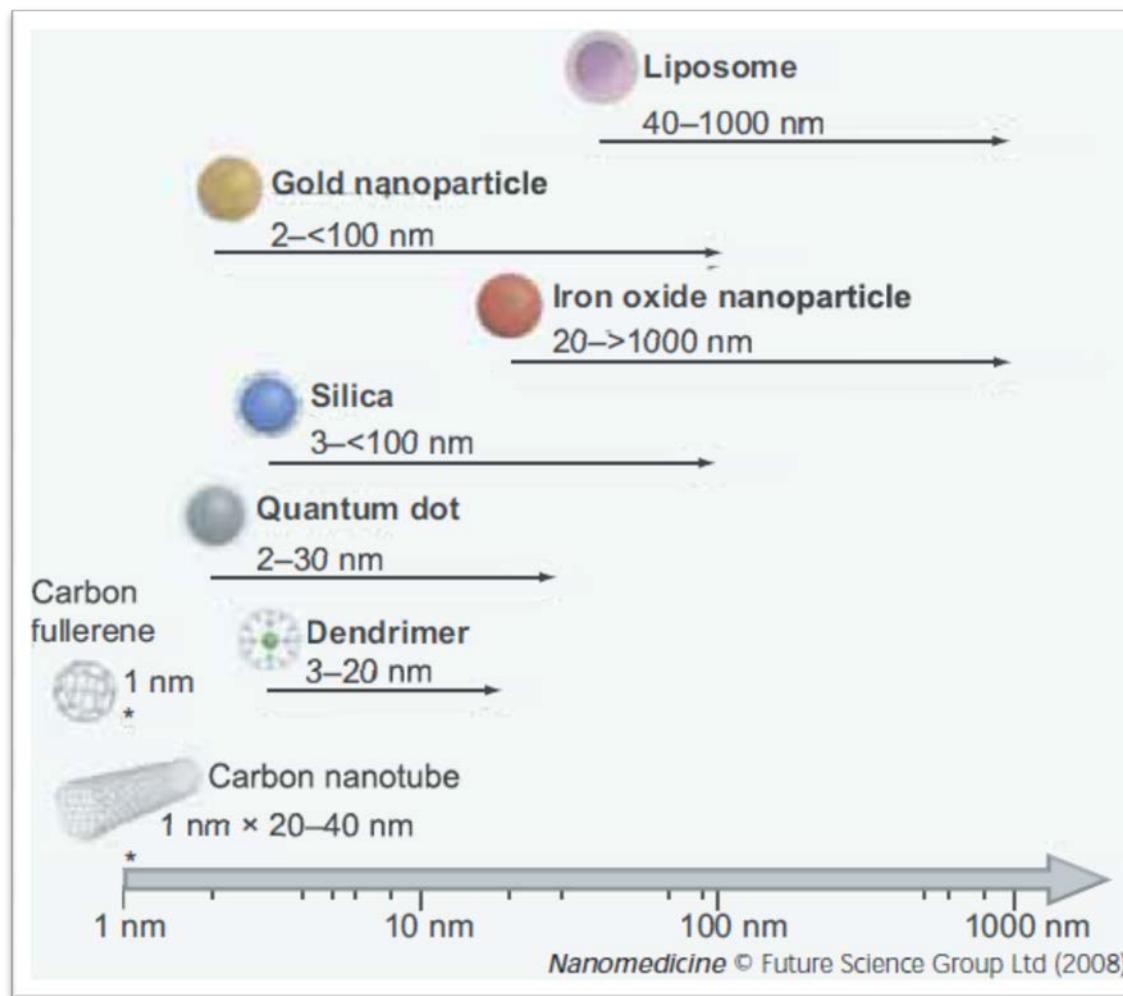


Clearance by kidneys

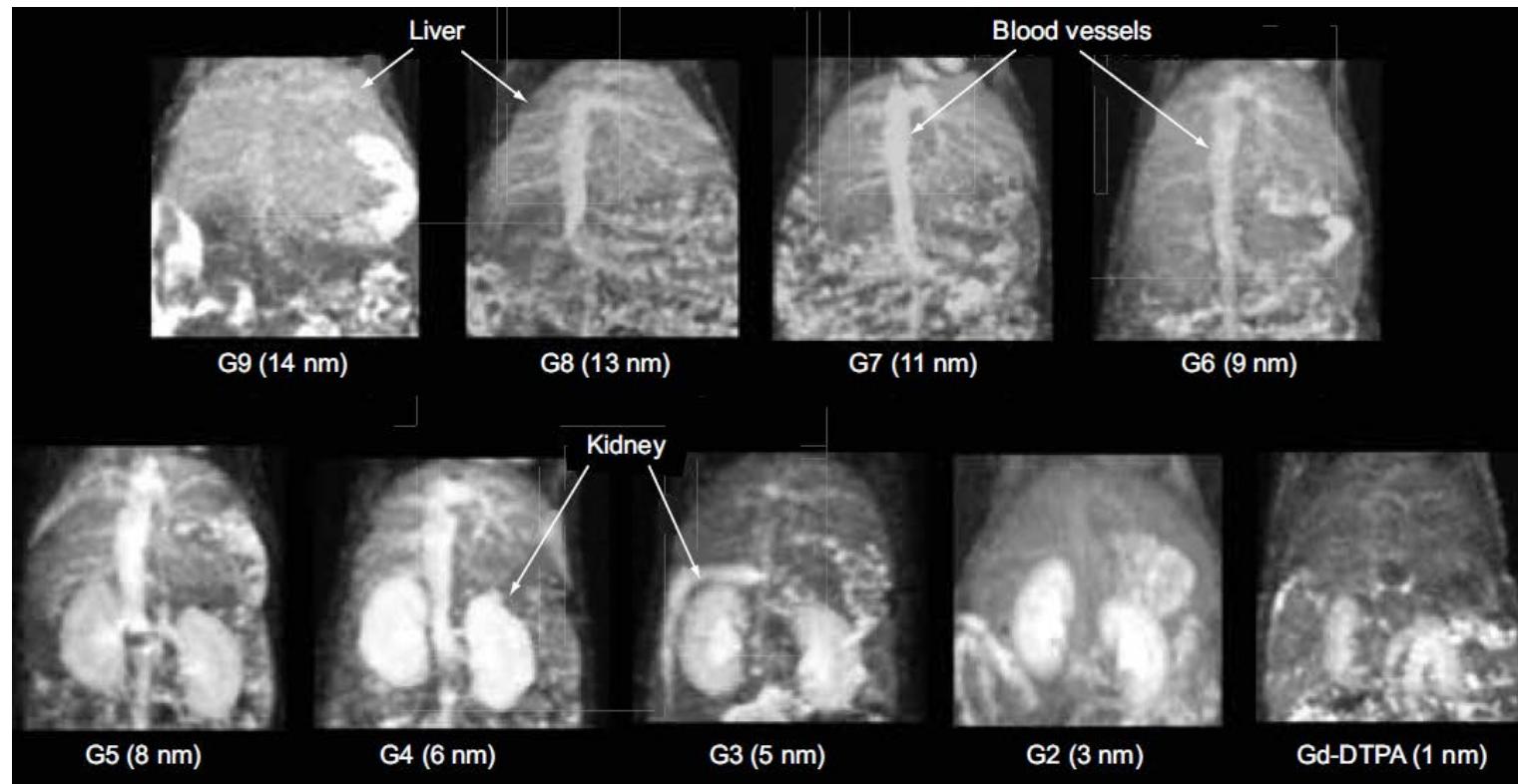
- Proteins with $D_h < 5 \text{ to } 6 \text{ nm}$ are freely filtered by the glomerulus
- Factors affecting deformability, such as hydration, flexibility as well as intra- and intermolecular architecture, therefore highly influence their glomerular filtration (polymers, soft matter)
- Hard NPs



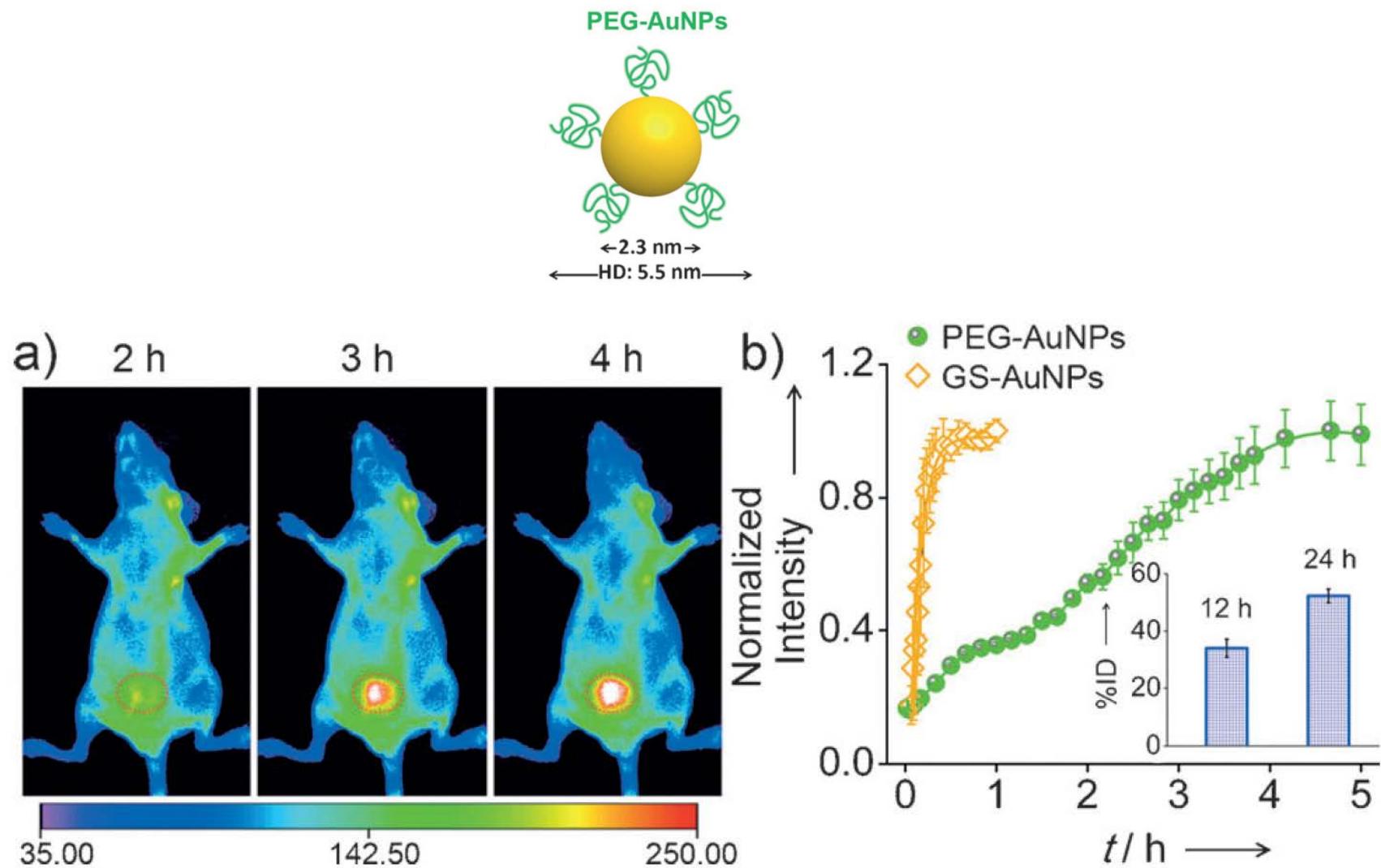
Chemical composition, size range and shape : determinants for clearance



3D maximum intensity projection display of T1-weighted MR images of the abdomen at 15 min. post-injection for G9, G8, G7 and G6 and at 3min. for G5, G4, G3, G2 and DTPA

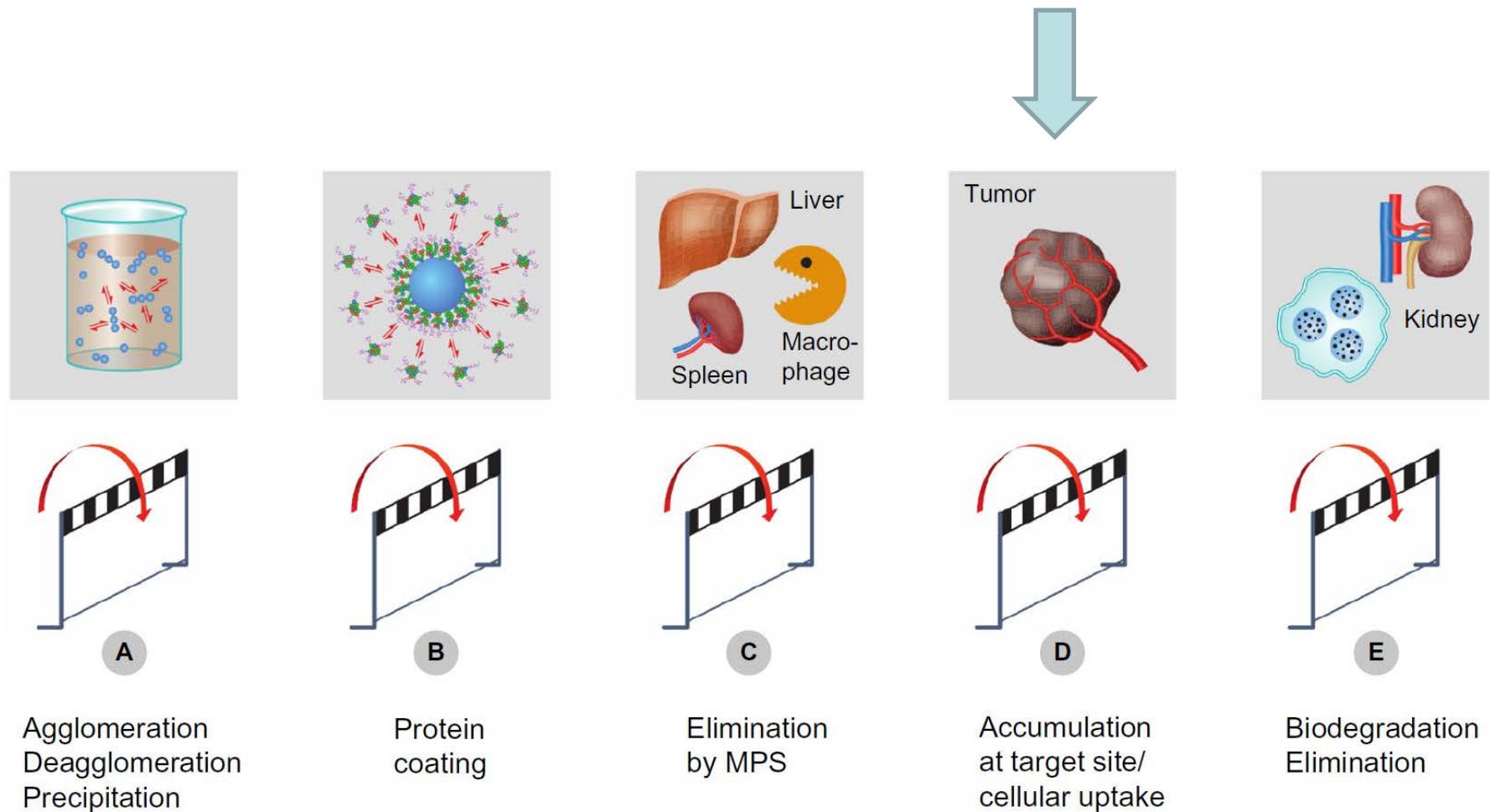


M. Longmire et al., Nanomedecine (2008) 3,5, 703-717



Clinical relevance:

- Risk of NPs accumulation in organs (liver, ...)
- if cancer : balance between a rapid clearance and a high tumor/normal tissue ratio
- clearly important in the case of contrast agent :
 - Development of NPs or nanosized molecule with favorable clearance properties
 - Renal filtration : preferred pathway (lower risk of retention), speed
 - Alternative route : intracellular degradation ?

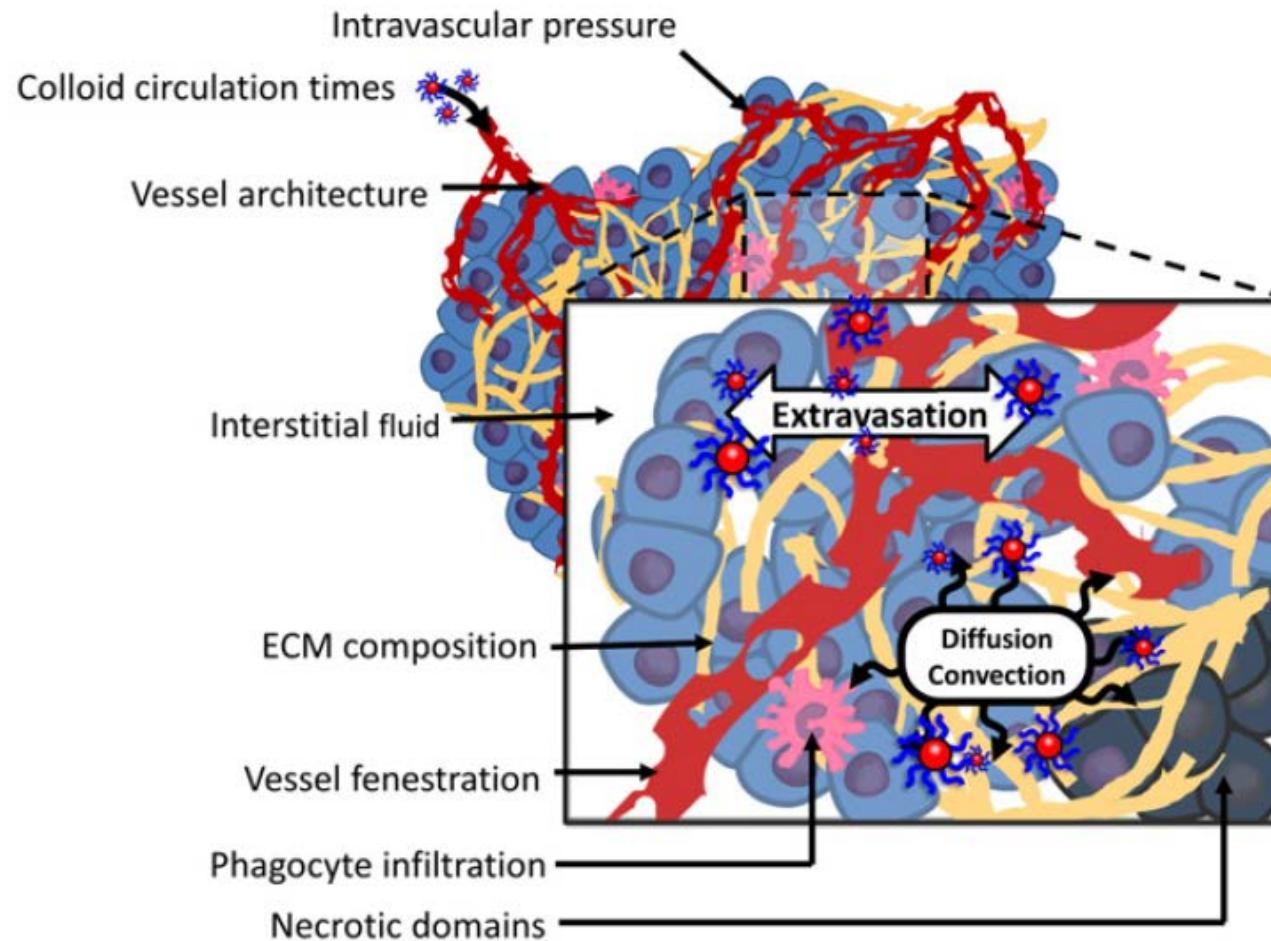


The Enhanced Permeability and Retention (EPR) effect

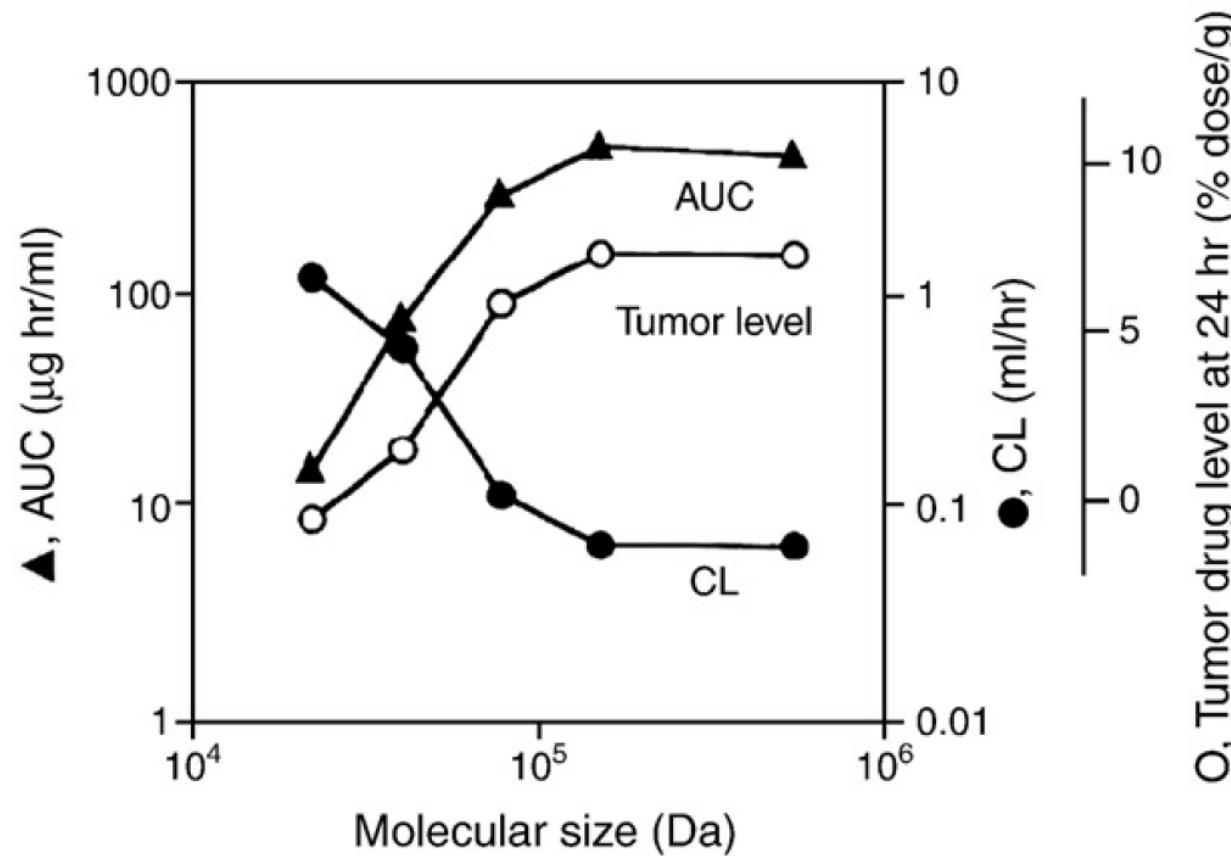
Reported by Matsumura and Maeda in 1986

- most solid tumors have blood vessels with defective architecture
- produce extensive amounts of various vascular permeability factors
- exhibit enhanced vascular permeability, which will ensure a sufficient supply of nutrients and oxygen to tumor tissues for rapid growth.

The EPR effect considers this unique anatomical–pathophysiological nature of tumor blood **vessels that facilitates transport of macromolecules into tumor tissues**

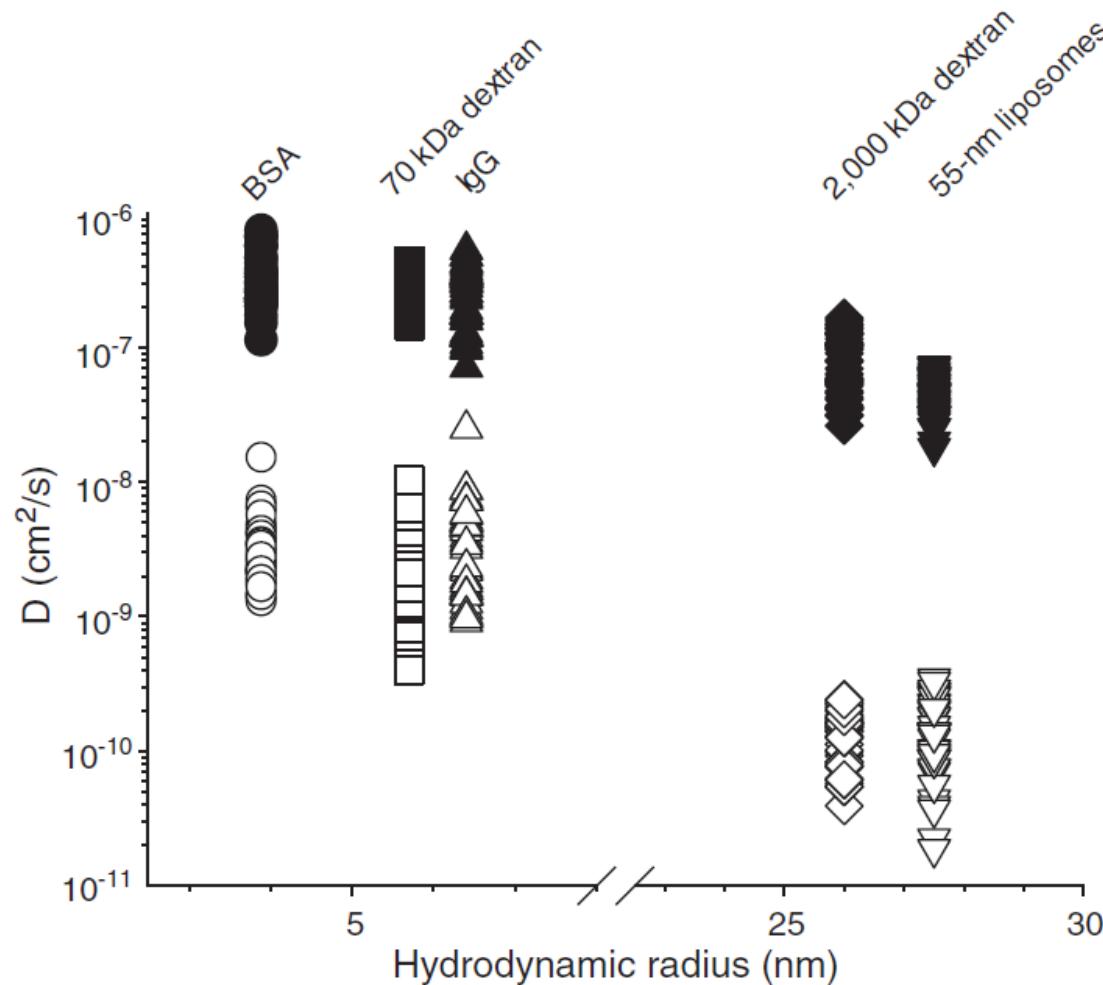


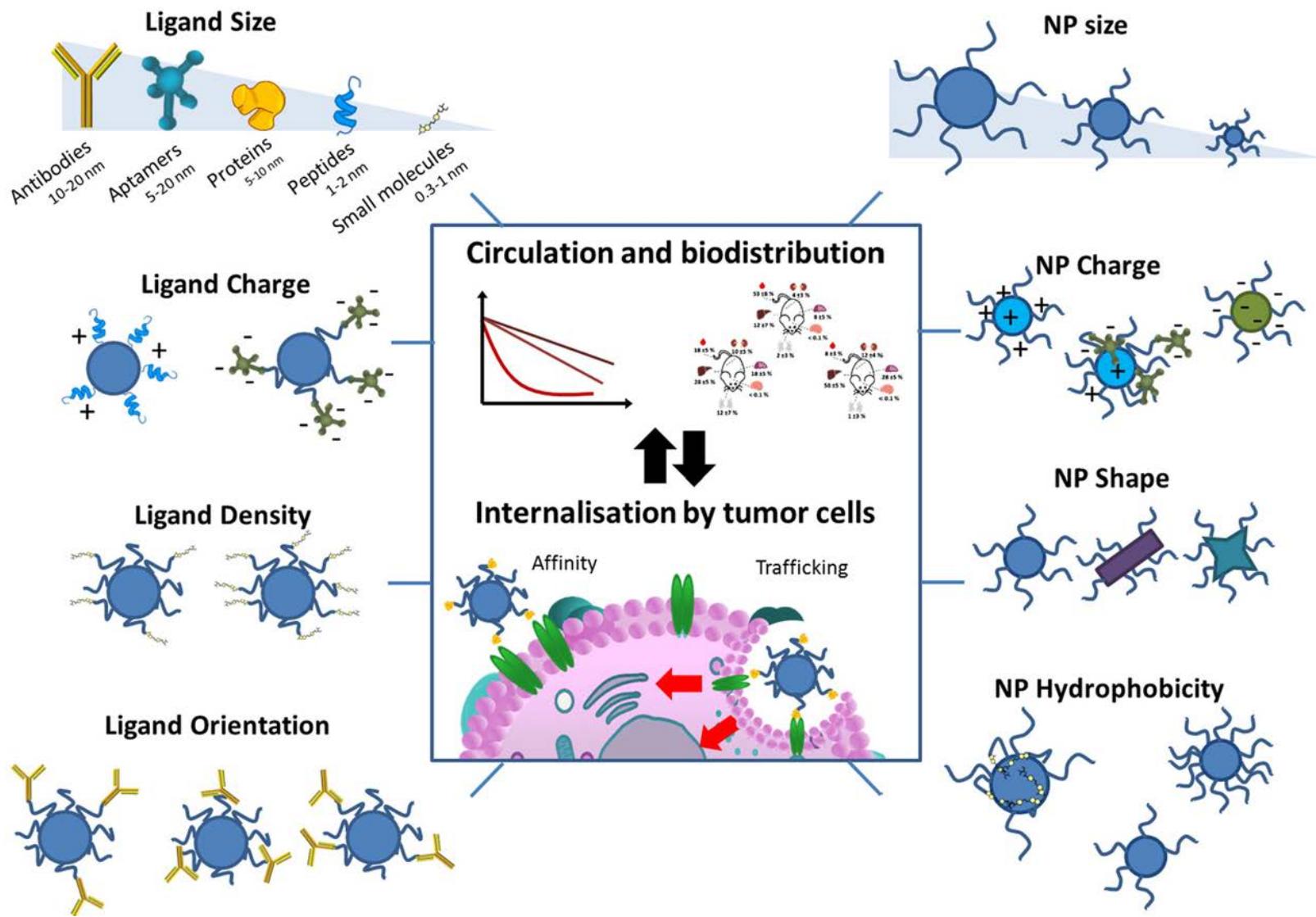
Relationship of the molecular size of drugs to plasma drug concentration (AUC), renal drug clearance (CL) and intratumor drug uptake



L.W. Seymour et al., Eur. J. Cancer 31A (1995) 766–770.

The diffusion coefficient of macromolecules and nanomaterial in the ECM is inversely proportional to the hydrodynamic radius





Proposed strategies to drug targeting:

PASSIVE

Relies on physiological body features, e.g.:

- Reticulo-endothelial system (RES).
- Monocyte-macrophage system.
- Enhanced Permeability & Retention (EPR) effect.

INVERSE

By blockage or saturation of passive targets.

- RES blockage by sugar polymers or lipid microemulsions.

ACTIVE

Based on imposing targeting properties to the drug:

- Intrinsic: drug designed to target a specific molecule.
- Extrinsic : drug coupled to targeting features
 - *Physical targeting: programmed release (temperature, pH, etc).
 - *Ligand-based: coupling to affinity moieties (as conjugates or through carriers).

COMBINED

By combining any of the other strategies, e.g.:

- Ligand-based targeting + physical targeting.
- EPR effect + ligand-based targeting.
- EPR effect + ligand-based targeting + physical targeting.

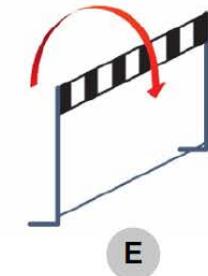
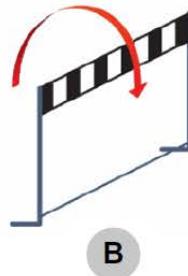
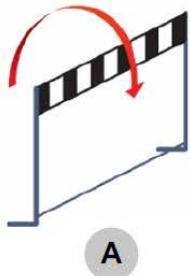
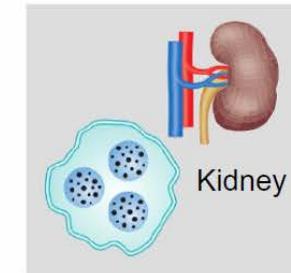
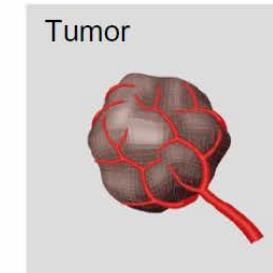
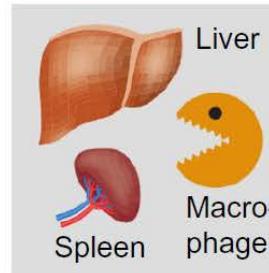
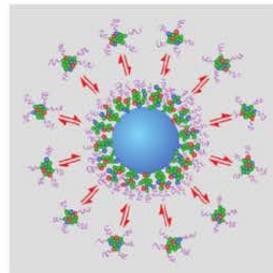
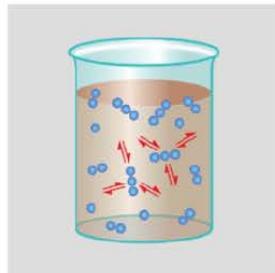
Key factors regarding to :

The nanocarrier :

- encapsulated drug
- structure and components of nanocarriers
- PEG-surface density and PEG-chain length
- size and surface charge

The administration :

- time interval
- third dose
- lipid dose
- route and mode of administration
- animal species



Agglomeration
Deagglomeration
Precipitation

Protein
coating

Elimination
by MPS

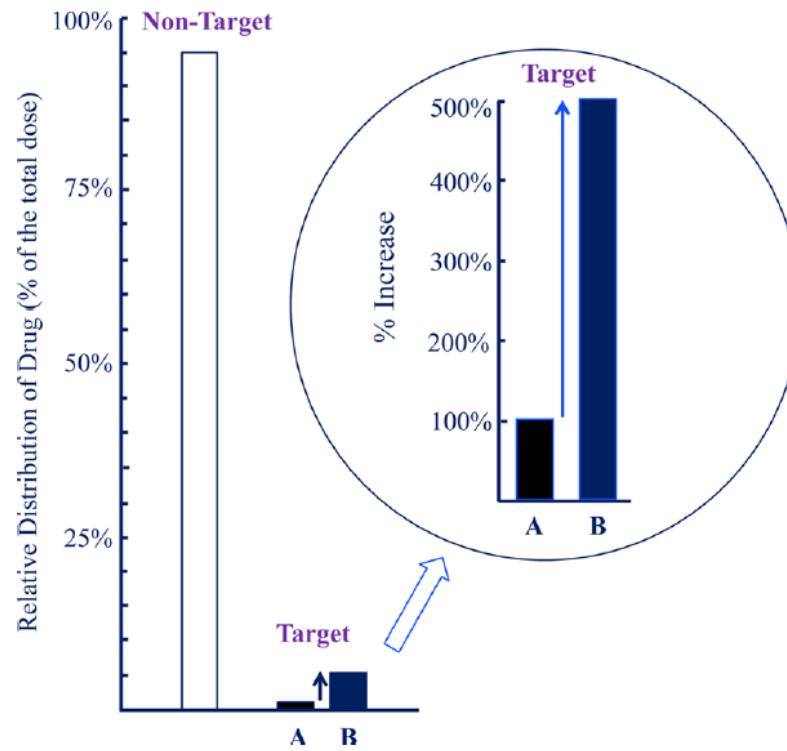
Accumulation
at target site/
cellular uptake

Biodegradation
Elimination



Moving to the clinical aspects

Relative distribution of a drug at a target tumor site by (A) conventional solution formulation and (B) nanoparticulate formulation.

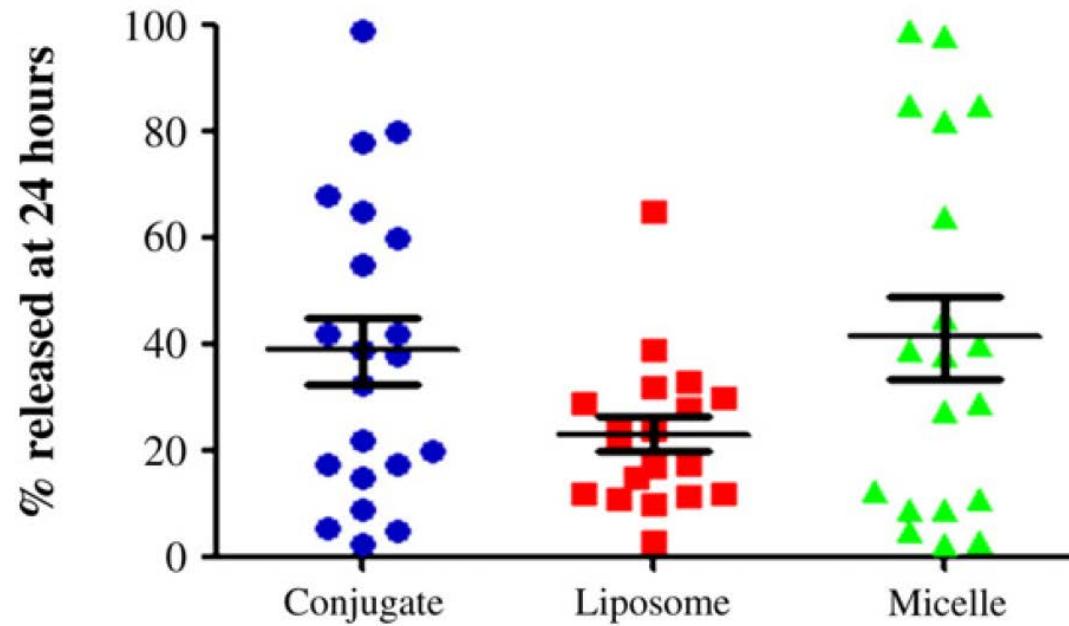


The majority of the administered drug ends up at nontarget sites, but the 5x more efficient delivery of the drug by nanoparticles can be exploited for maximizing drug efficacy

... into more details:

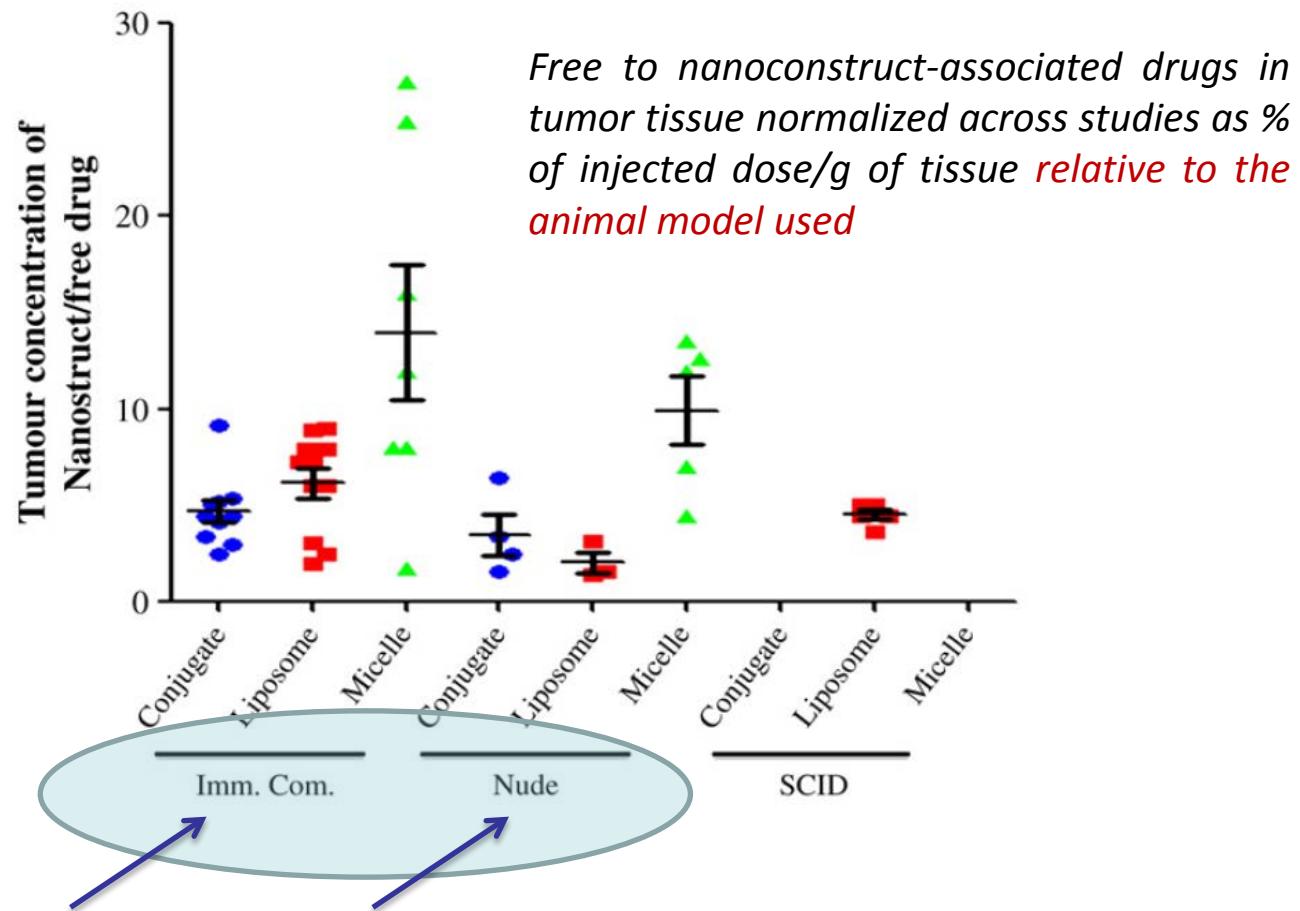
The release rate

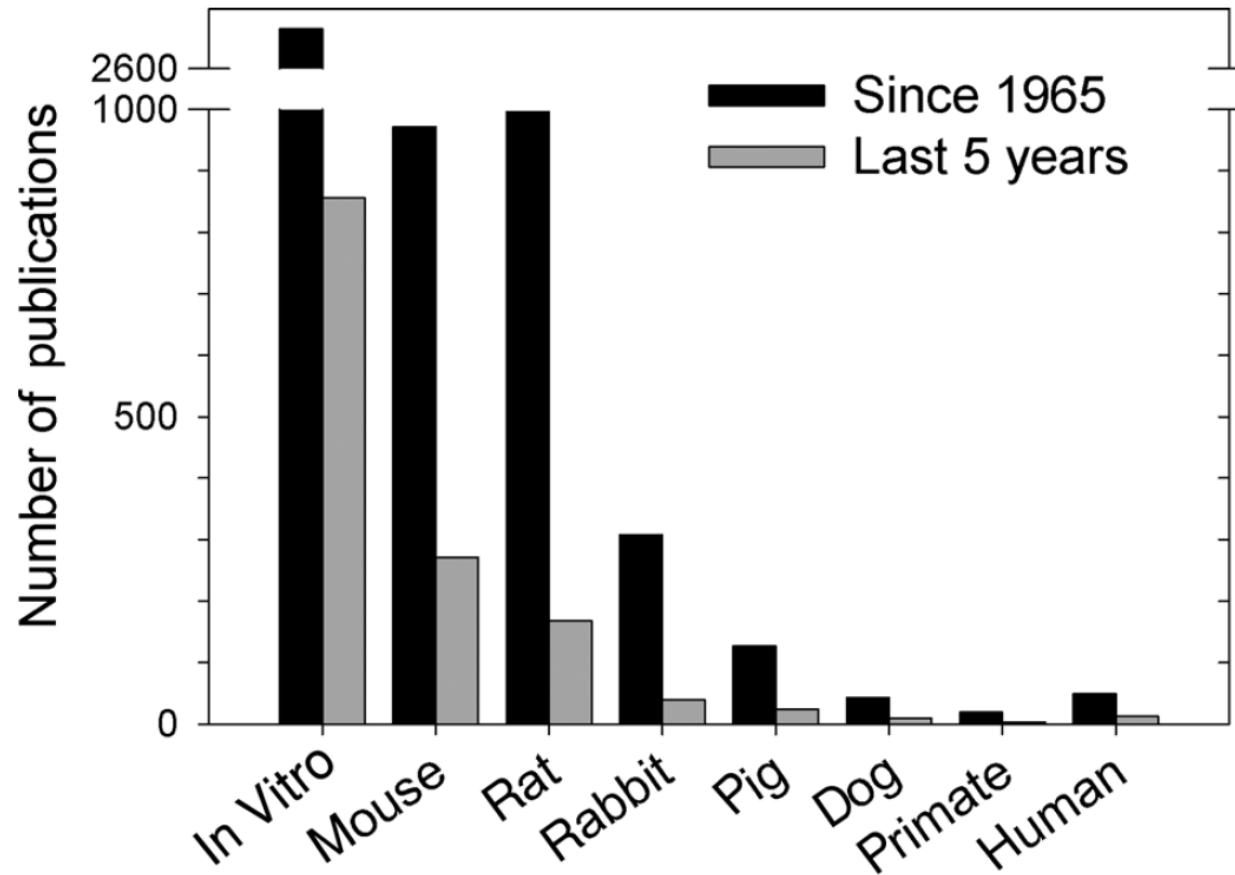
over a 24 h period for different nanocarriers



Validation of tumor models

Question : can the results of EPR-based drug targeting in animal models be faithfully translated to the clinic ?
no clear answer....





Kraft et al., JOURNAL OF PHARMACEUTICAL SCIENCES 103:29–52, 2014

- Lack of uniformity in pre-clinical trials of nanoparticle-based delivery systems**
- Few report quantitative data on parameters that would be useful in developing design rules for nanomedicines**
- The poor experimental design and variability of experimental conditions**



Lack in the clinical impact of such preclinical studies

Summary of limitations to pre-clinical studies of nanomedicines

Total tumor accumulation (%ID) is not always reported

Inconsistent reporting of tumor size/weight Report tumor size/weight

Inconsistent reporting of dose

Inconsistent reporting of physico-chemical properties

Report tumor accumulation as %ID (and %ID/g)

Report drug loading, drug concentration (and/or drug amount), and activity of dose (gamma counter)

Report standard physico-chemical properties (e.g., size, zeta potential, surface coating, stability under physiological conditions)

Summary of limitations to pre-clinical studies of nanomedicines (2)

Tumor accumulation reported at different time points

Report tumor accumulation at standard time points (e.g., 1 and 24 h post-injection). Detailed pharmacokinetics (concentration in blood and tumor) at multiple time points is preferred

Variation in tumor characteristics (type, size, vascularization, etc.)

Standardize tumor type and size - More difficult for active targeting depending on target molecule

Variation in controls used in active targeting

Report control studies for delivery system with no targeting ligand and any differences in physico-chemical properties. Report other control studies as necessary

Summary of limitations to pre-clinical studies of nanomedicines (3)

Variation in animal models (mouse, rat, etc.)
and differences in drug concentration
compared to humans

Animal model : crucial need

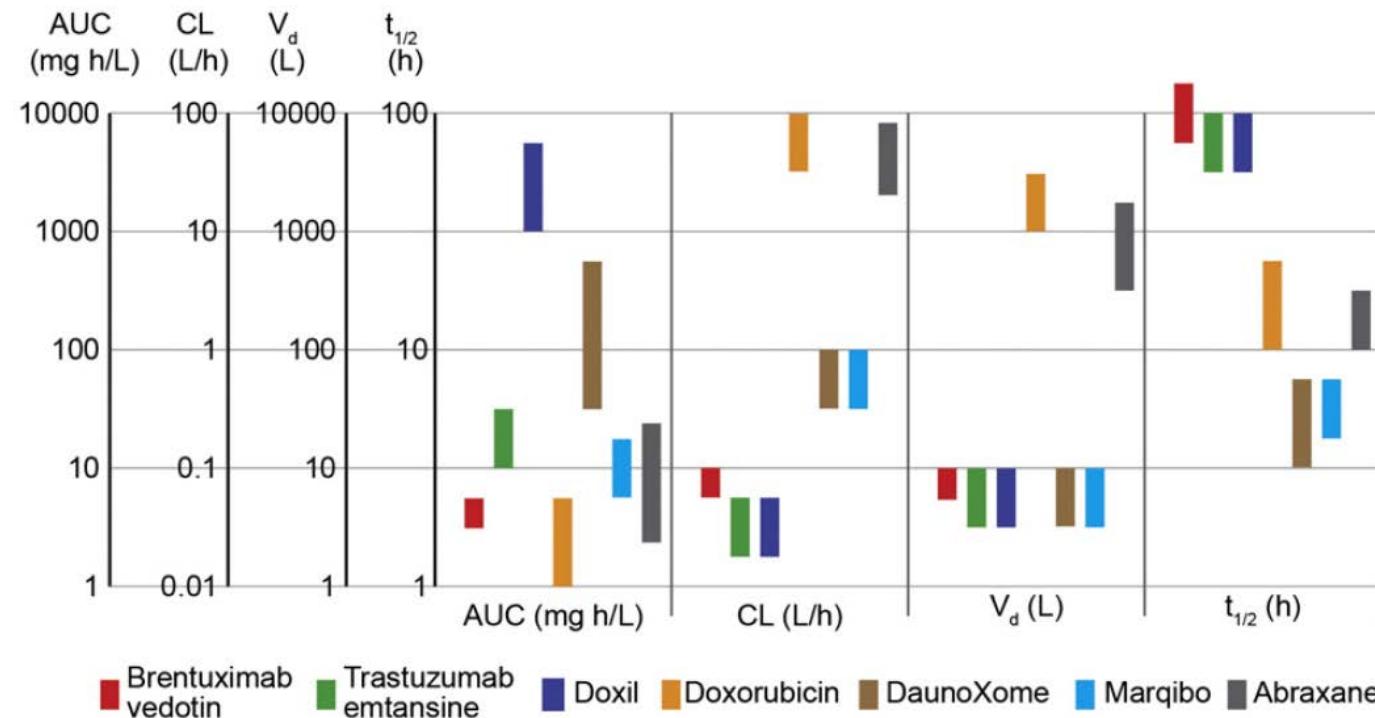
Different detection methods used to assess
tumor accumulation

Needs validation!

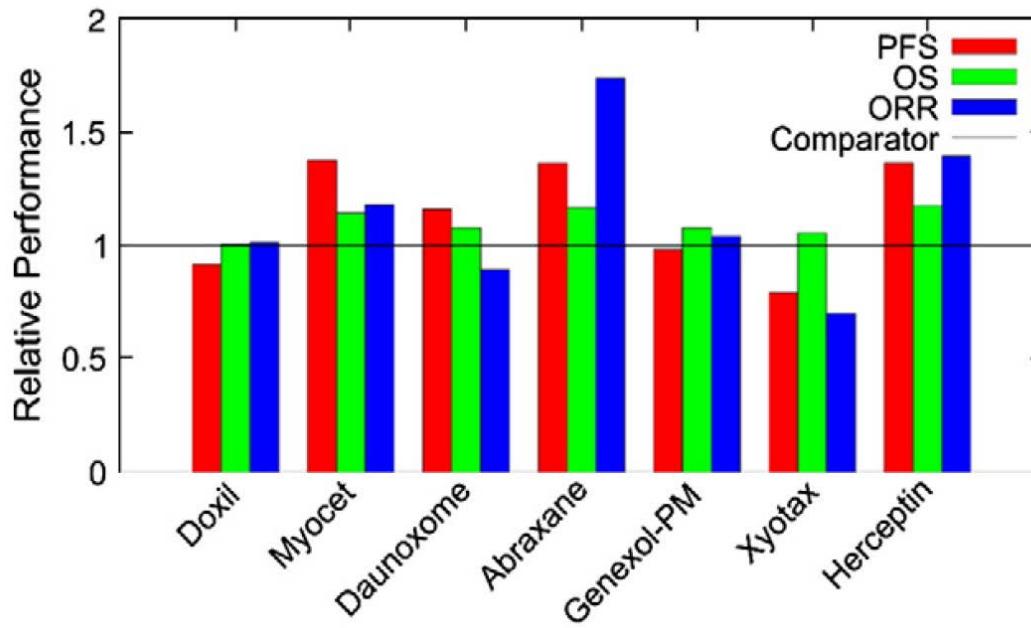
Nanotechnology-based DDS and PK

Formulations are unique in the way it changes the interactions between the drug and body

... leading to different pharmacokinetic parameters such as half-life, area under the curve, distribution, and clearance



... and clinical efficacy is rarely reported !



Phase III:

PFS: progression free survival

OS: overall survival

ORR: overall response rate

EPR : clinical relevance

Doxil (Caelyx in EU) :

Best efficacy against ARKS and multiple myeloma vs conventional treatment

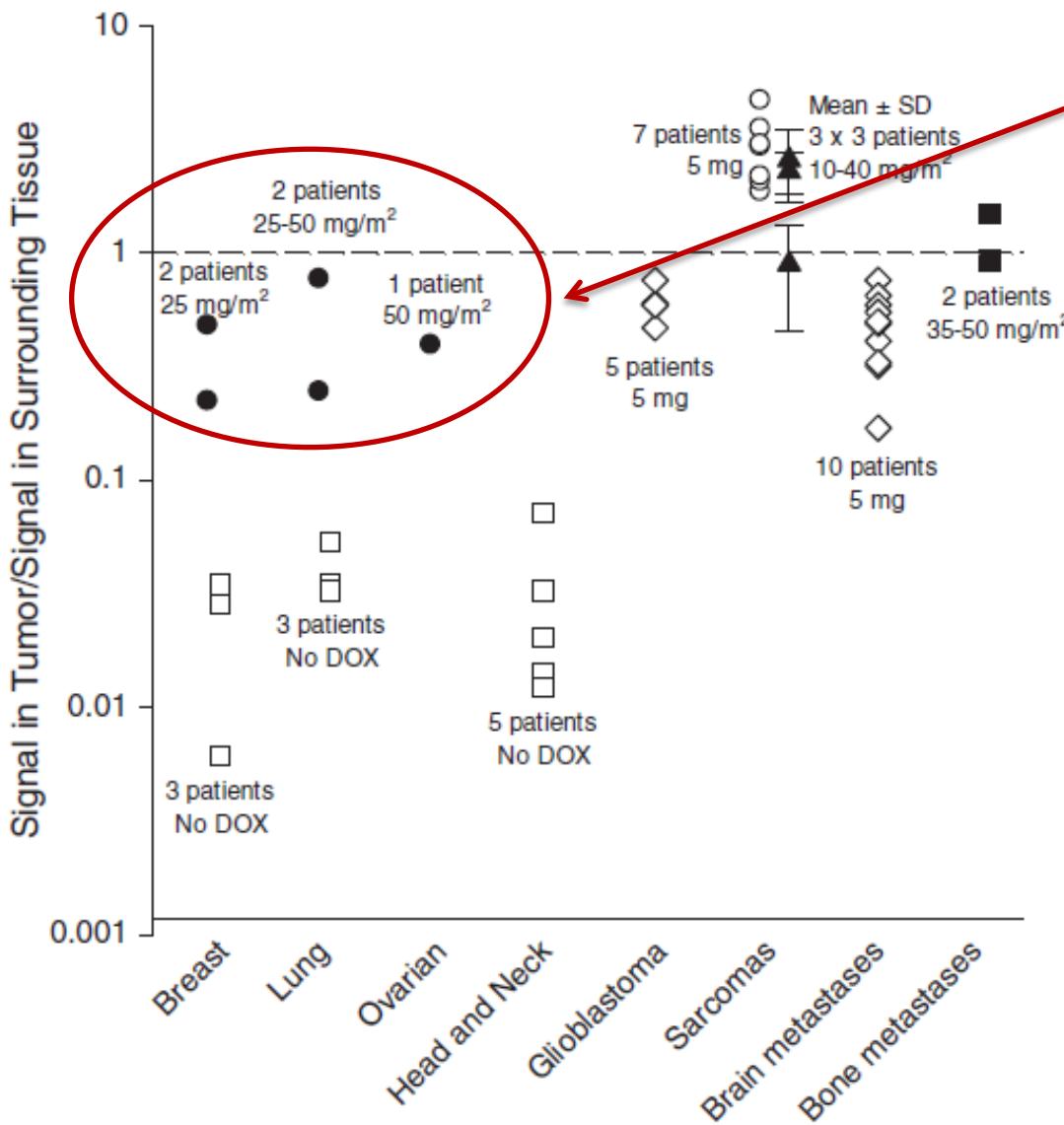
but...

- KS : blood vessels so leaky that red blood cells are able to easily escape, giving the tumor a bruise-like appearance
- Multiplemyeloma = liquid tumor comprised of excessively proliferating B-lymphocytes in the bone marrow but is still associated with very low IFP and significant neovascularization of the bone marrow

Doxil (Caelyx in EU) :

and ...

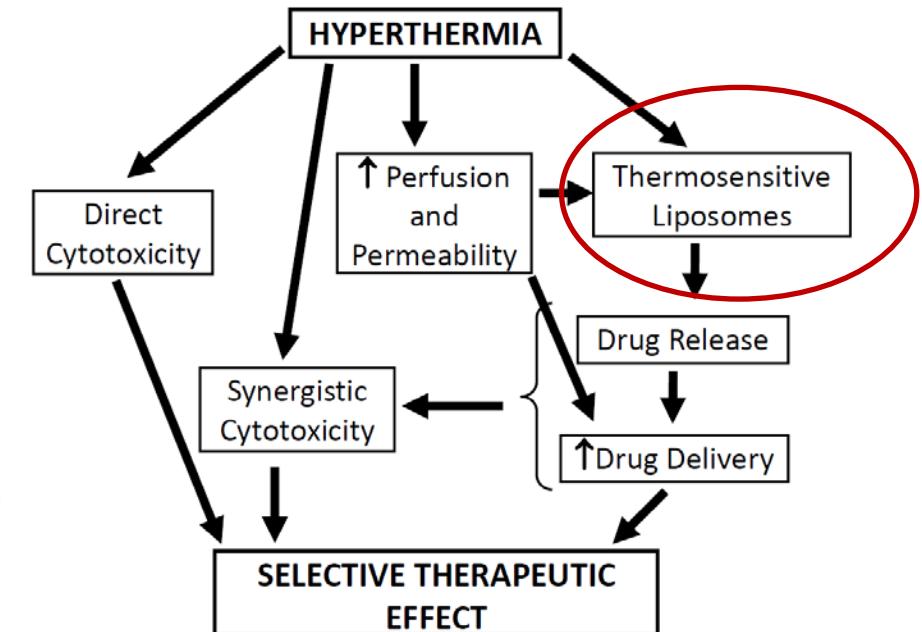
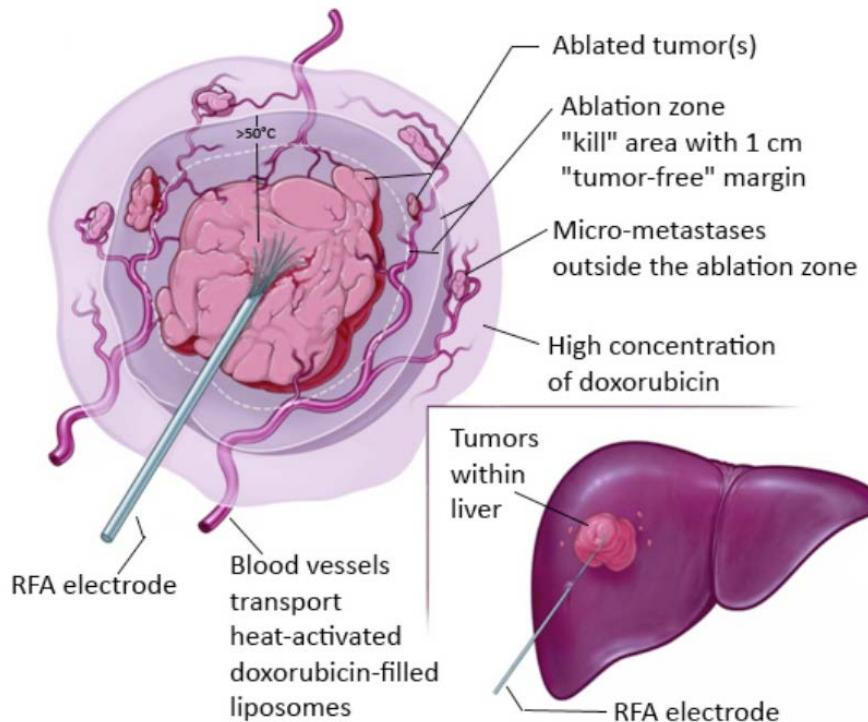
- appears to **improve efficacy concerning the biodistribution**, and is widely used in clinical settings on that basis
- while phase III trials including more solid tumors such as ovarian and breast cancer **failed to show significantly improved efficacy**
- main benefit of Doxil in treating solid tumors = reduced cardiotoxicity... but
- toxicity was aggravated in other categories, most notably skin toxicity in the form of hand and foot syndrome



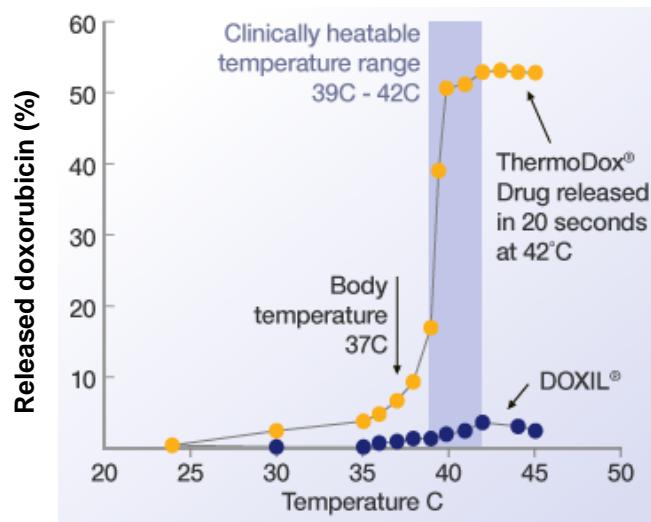
- (●) DOXconcentration in malignant infusion vs. plasma concentration, using Doxil®
- (□) 111In-DTPA-labeled liposomes in tumor ROI vs. plasma concentration.
- (◊) 99mTc-DTPA-labeled Doxil® tumor ROI vs. skull bone marrow.
- (▲) DOX concentration in tumor biopsies vs. plasma concentration, using DOX-containing PEGylated liposomes.
- (○) 99mTc-DTPA-labeled liposomes tumor ROI vs. surrounding tissue.
- (■) DOX concentration in bone metastases vs. plasma concentration, using Doxil®.

RF ablation : destruction of the central tumor mass by hyperthermia

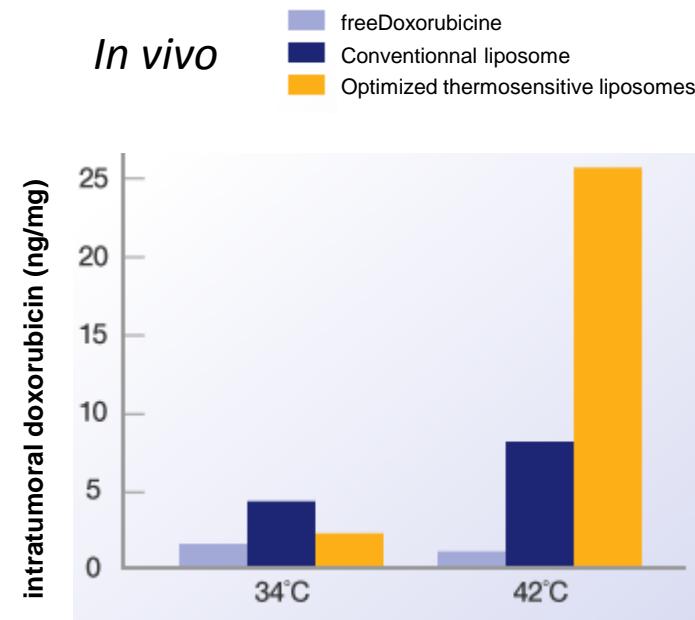
but temperature drops precipitously back to body temperature away from the heating locus, allowing microscopic deposits of tumor cells at the periphery to escape treatment



In vitro



In vivo

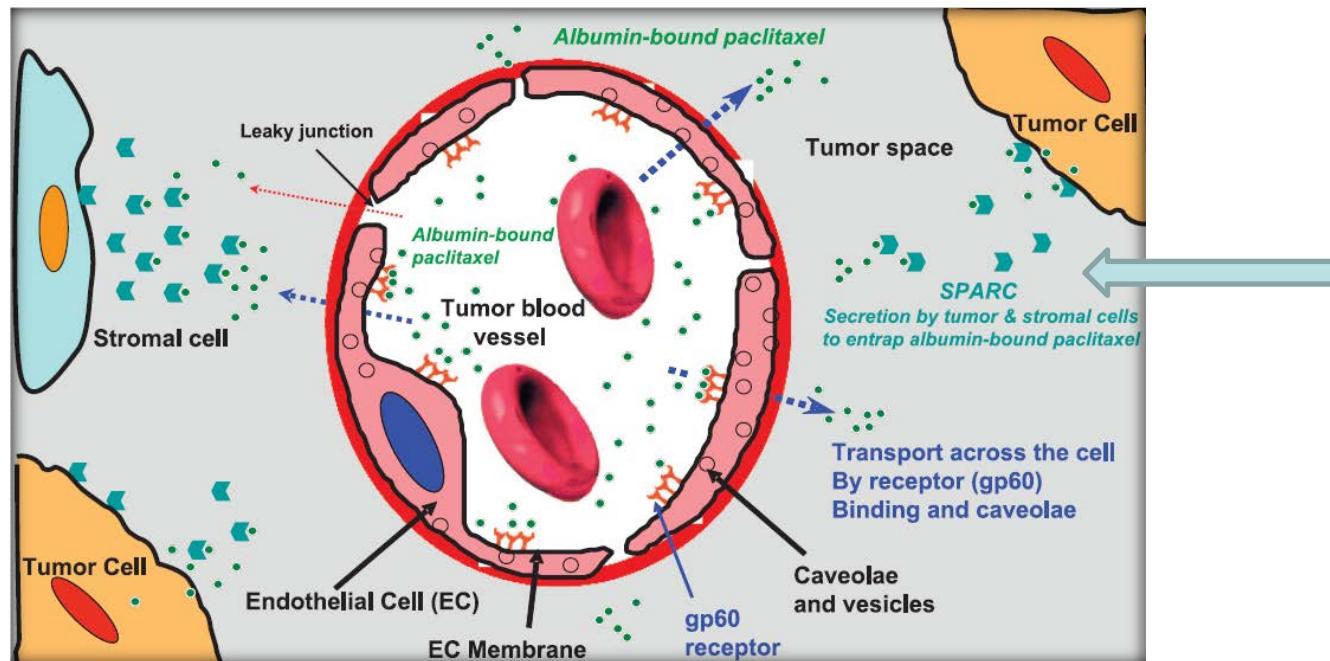


Intratumoral release of doxorubicin after 1h at 42°C

Celsion Announces Results of Phase III HEAT Study of ThermoDox® in Primary Liver Cancer

"We are disappointed that the HEAT Study did not provide sufficient evidence of clinical effectiveness of ThermoDox® as measured by the trial's primary endpoint," said Michael H. Tardugno, Celsion's President and Chief Executive Officer. "We will consider following the patients currently enrolled in the HEAT Study to the secondary endpoint, Overall Survival (OS), and are conducting additional analyses of the data from the trial in order to assess the future strategic value of ThermoDox..."

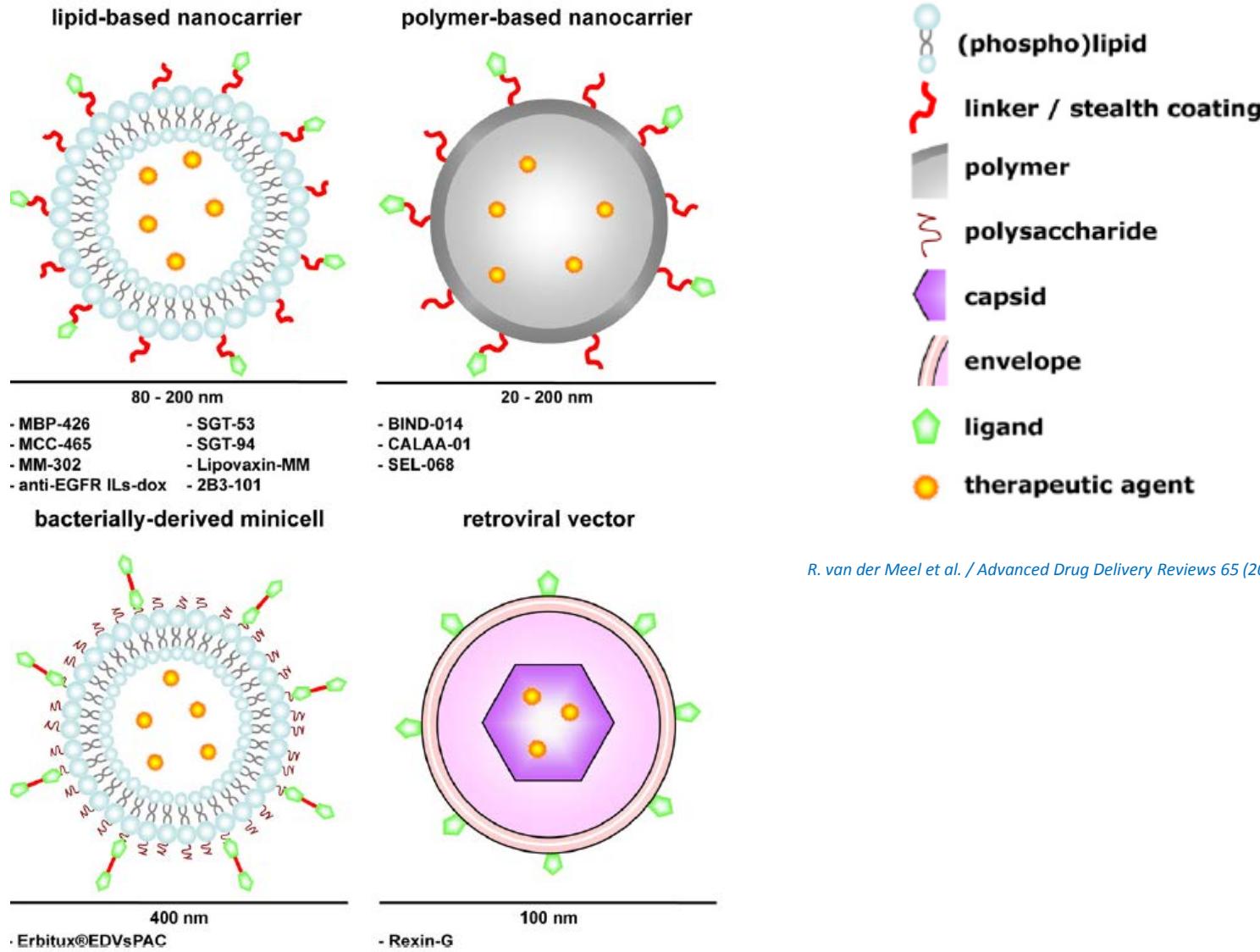
SPARC Expression Correlates with Tumor Response to Albumin-Bound Paclitaxel in Head and Neck Cancer Patients



N. Desai and al., *Translational Oncology* (2009) 2, 59–64

SPARC Status	Patients Responding	Patients Nonresponding
Positive ($n = 12$)	10/12 (83%)	2/12 (17%)
Negative ($n = 4$)	1/4 (25%)	3/4 (75%)

Ligand-targeted nanomedicines undergoing clinical evaluation



R. van der Meel et al. / Advanced Drug Delivery Reviews 65 (2013) 1284–1298

Thank you for attention

