

Basic considerations on the use of particles and polymers in molecular imaging

in "Chemistry in Contrast Media"

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Learning objects

- Non-targeted particles and polymers
- "Really" basic considerations
- Inspiration from nature's own particles
- Clearance pathways in relation to properties (e.g., PEGylation)
- Size aspects in relation to biological entities
- Immunogenic effects

Case by case for each polymer or nano-particle!!

Contents

- Basic consideration on nano-materials
 - "slow but powerful", unique properties...
 - Bio-degradable?
- Pharmacokinetics (PK) of nano-sized agents
 - Size
 - Beyond size
 - charge, hydrophilicity, surface-coating, flexibility
 - Nano-toxicology
- Interaction with protein
- Immunogenicity

Small vs Large

Small molecules



Bikes: Fast but less powerful

Polymer and nano-materials



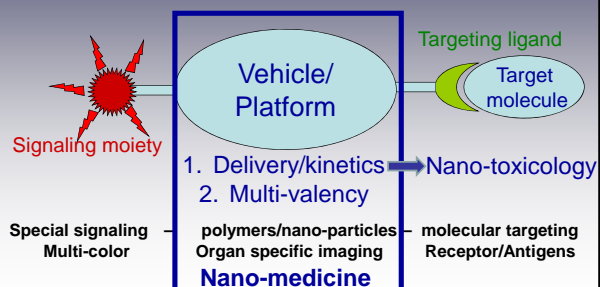
Tracks: Slow but powerful

Can be faster, safer, or more powerful???

Unique signaling

Nanomedicine for imaging

Imaging probe design

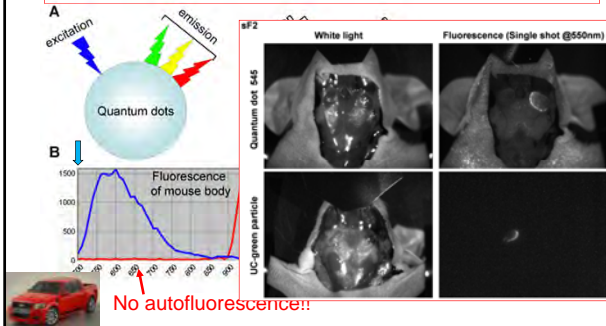


Quantum dots can emit multiple color of light with single excitation

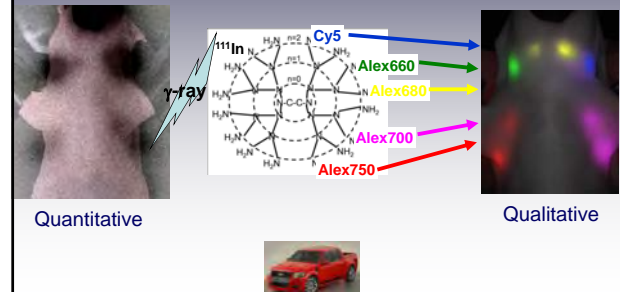


Upconverting Nano-crystals (UCNC)

can emit shorter wavelength of light than excitation light.
can realize imaging without background auto-fluorescence.



Dendrimer can be used as a dual-modal & multi-color platform



Biodegradable?

Non-biodegradable

- Generally a covalently-bonded single molecule without enzyme for catabolism.
- PK: an injected molecule simply behaves depending on its physical and chemical characteristics.

Biodegradable

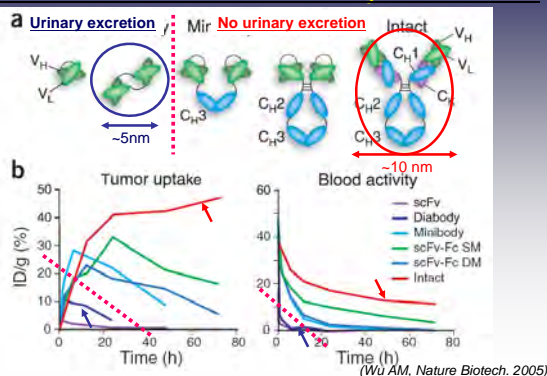
- A molecule with cleavable bonds, or a self-assembled crystal or particle consisting of multiple molecules or ions
- PK: **complicated!!** because all intermediate and final catabolites can behave differently in the body.

➡ To explain the basic strategy, I only discuss the behavior of non-degradable molecules/reagents.

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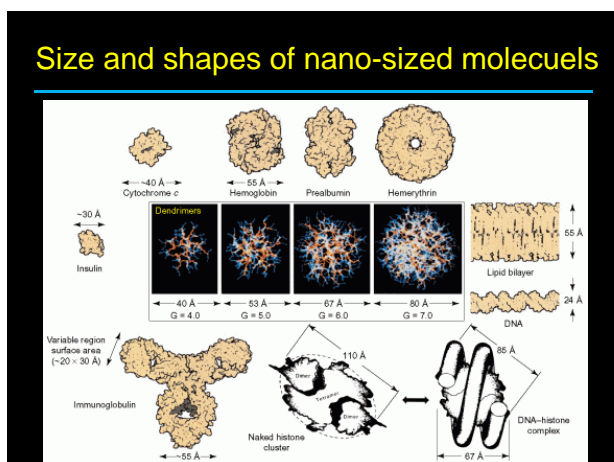
We learned PK of nano-sized agents a lot from radio-labeled antibody studies



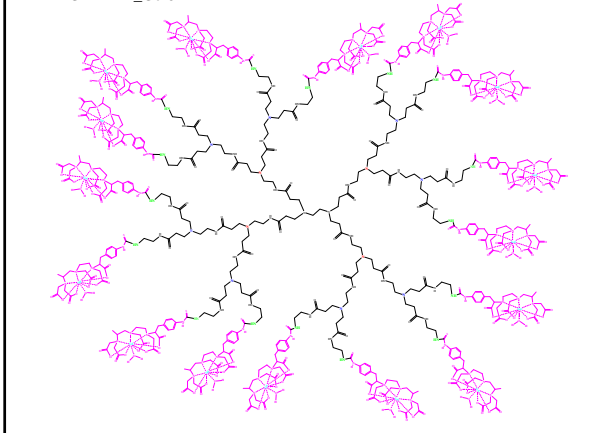
Pharmacokinetics of nano-sized agents

- Size
- Beyond size
 - Charge
 - Hydrophilicity
 - Hard/soft – shape/flexibility
 - Binding or association with serum proteins

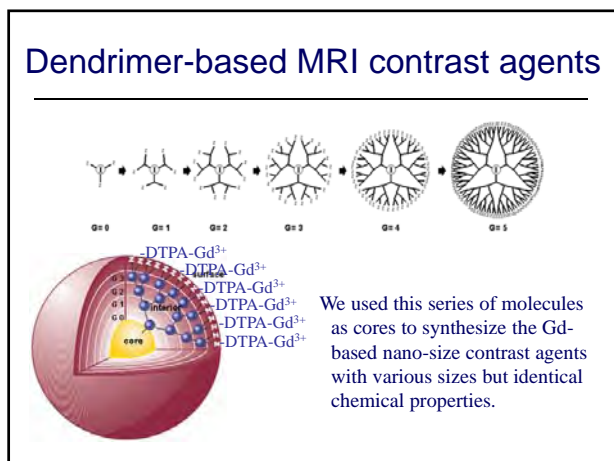
Size and shapes of nano-sized molecules



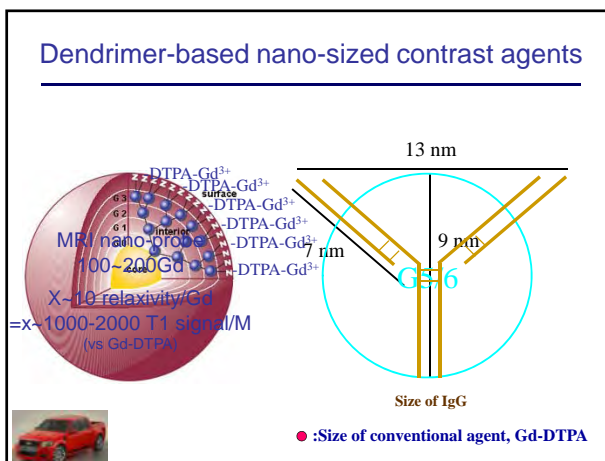
PAMAM G2-1B4M_Gd 01



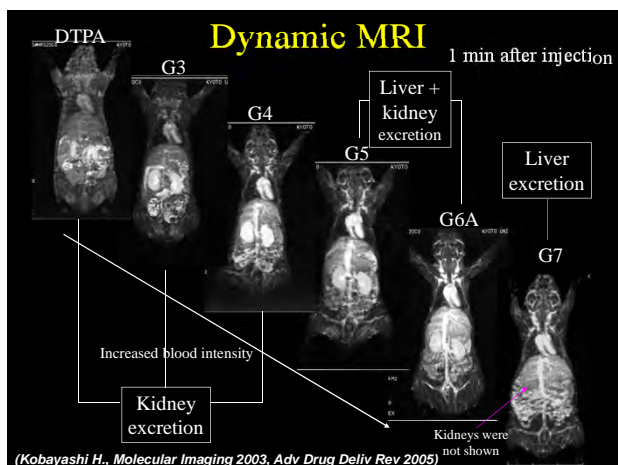
Dendrimer-based MRI contrast agents



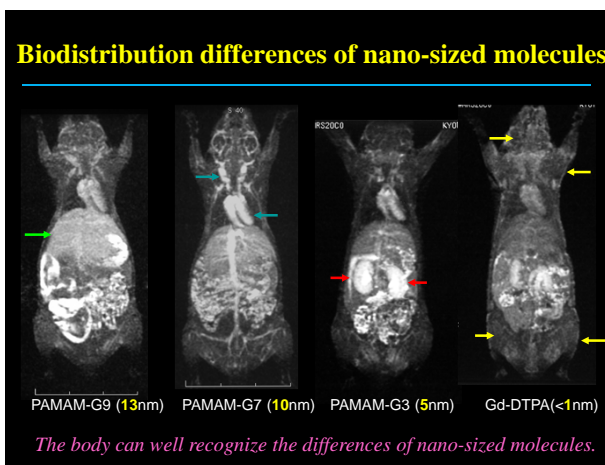
Dendrimer-based nano-sized contrast agents

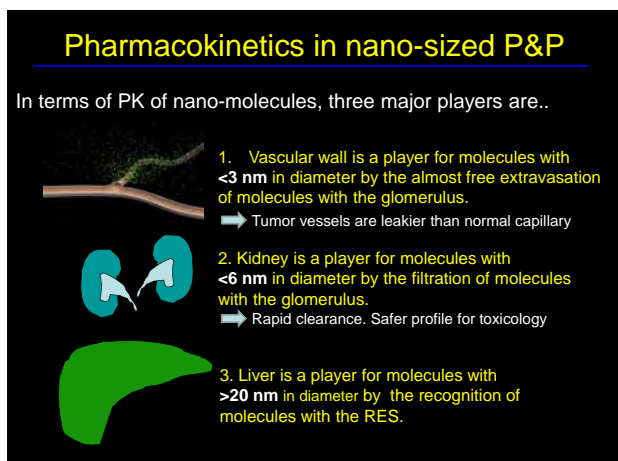
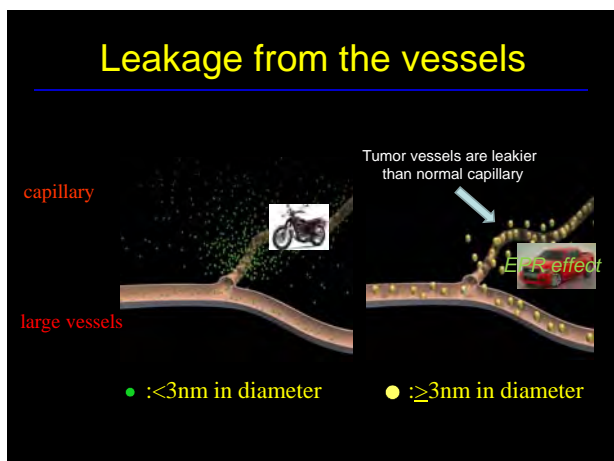
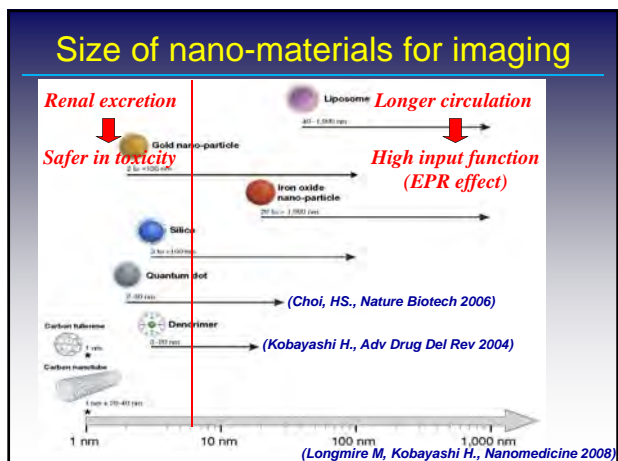
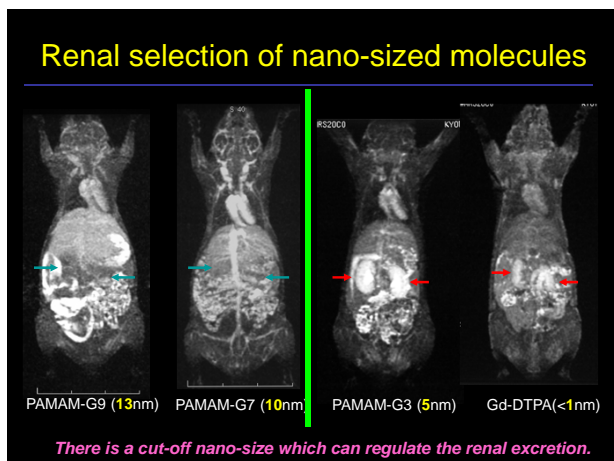
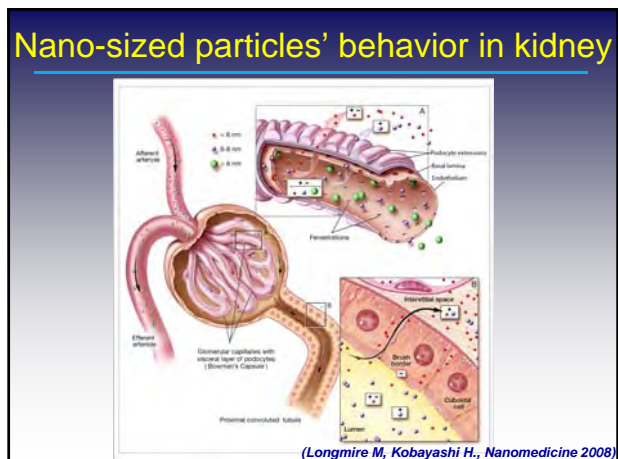
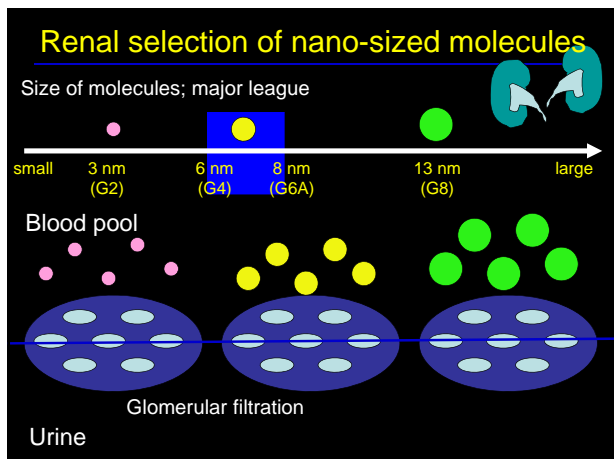


Dynamic MRI



Biodistribution differences of nano-sized molecules

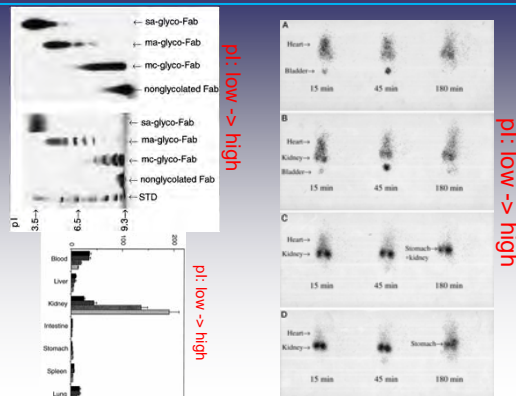




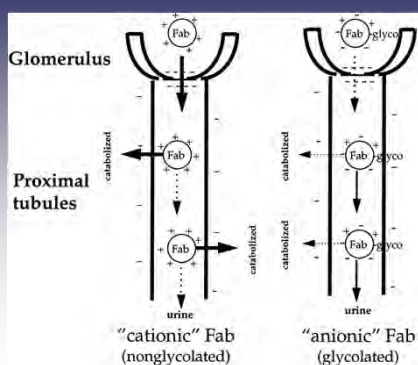
Beyond size

Charge

PK change of Fab (~6nm) by charge



PK change of Fab (~6nm) by charge

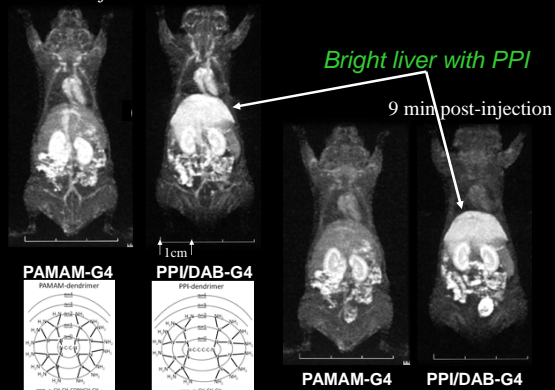


Beyond size

Hydrophilicity
(Stealthy from RES)

Different interior PAMAM to PPI change PK

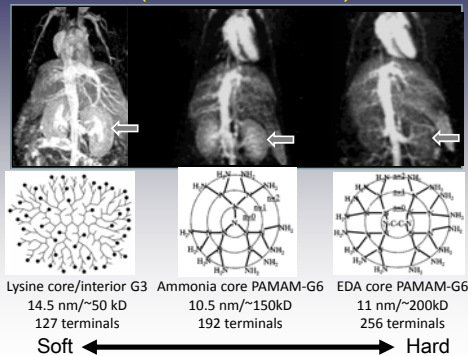
1 min after injection



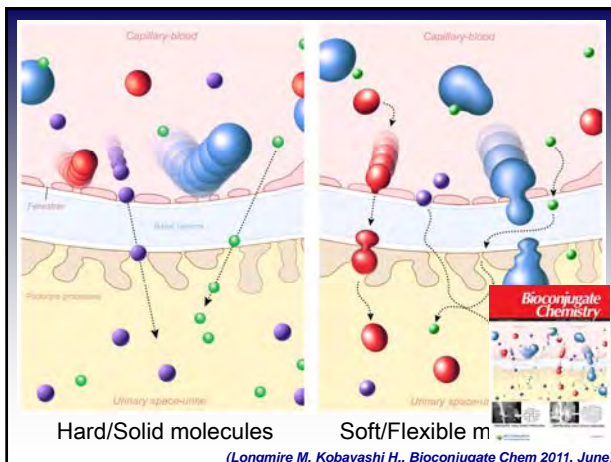
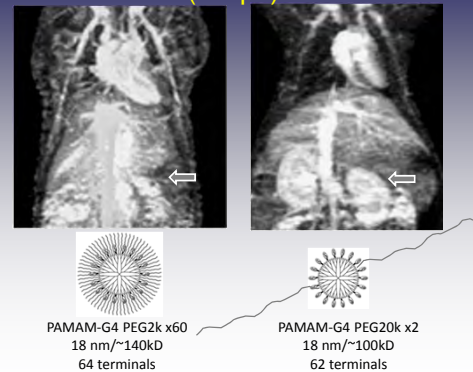
Beyond size

Hard/soft – Shape/Flexibility

PK of nano-materials beyond size (hard/soft interior)



PK of nano-materials beyond size (shape)



Contents

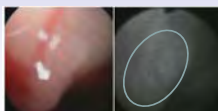
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Binding or association to protein

Strong binding

- Behave like a single larger molecule
- Longer clearance from the circulation

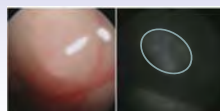
Immunogenicity might increase in both case



EPR effect
as a large single molecule

Weak association

- Partially behave like a single larger molecule in short term
- Clearance does not change much



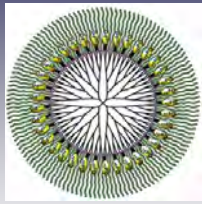
Partial EPR effect
with fast clearance

Immunogenicity

- Immunogenicity of nano-sized agents is Yes or No answer, yet is really case-by-case and hard to be predicted.
- Lowering immunogenicity: surface coating
 - Well hydrophilic (*i.e.* PEG)
 - Neutral or a little anionic surface charge

- Less interaction with immune cells
- Less opsonization

Hydrophilic (PEG) surface coating



Plasma half life = 12 h



Plasma half life = 0.3 h

Hydrophilic coating induces stealthy of nano-sized molecules/ particles from RES

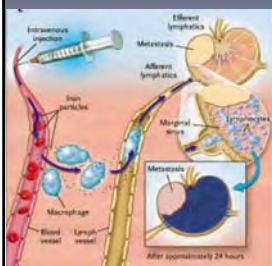
(Kojima C, Kobayashi H., Int J Pharm. 2010 and many others)

Summary

- Nano-materials with relatively small size can be **excreted through kidneys into urine**, resulted in **preferable profile** for the **nano-toxicology**.
- The **in vivo delivery and BioD** of nanomaterials can be **controlled** by simply changing the **physical and chemical characteristics** (size, shape, charge, flexibility, hydrophilicity, surface coating, etc.).
- Long circulation** due to stealthy from RES is important for tumor delivery based on EPR effects
- Signal** obtained from nano-materials can be **unique** for depicting new organs or targets, which currently cannot be visualized.

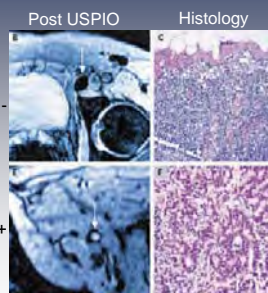
Lymph node imaging

Mechanism



Mets -

Mets+



(Harisinghani MG, et al; N Engl J Med.2003)

Dynamic MR lymphangiography of a pig

(G6-dendrimer agent: 1 $\mu\text{molGd/kg}$)



Optical lymphatic flow imaging using ICG

*ICG is an FDA-approved fluorophore.
ICG can bind to serum protein and behave like an macromolecule in vivo.*



(Sharma, Sevvick-Muraca, AJP Heart 2007)



(Troyan, Frangioni, Ann Surg Oncol 2009)

Take home messages

- Nano-material** (polymers or particles) can have nearly **infinite possibilities** for developing new imaging agents.
- Precise control of size, shape, charge, hydrophilicity, and flexibility allows us to optimize the target-delivery and pharmacokinetics of imaging agents in the body that can **improve imaging** and **lower nano-toxicity**.
- Unique signaling characteristics allows us to perform a variety of **multiplexed imaging**, which can extract **more comprehensive information** from the living body than conventional imaging.