Bridging Multiple Scales in Modeling Targeted Drug Nanocarrier Delivery

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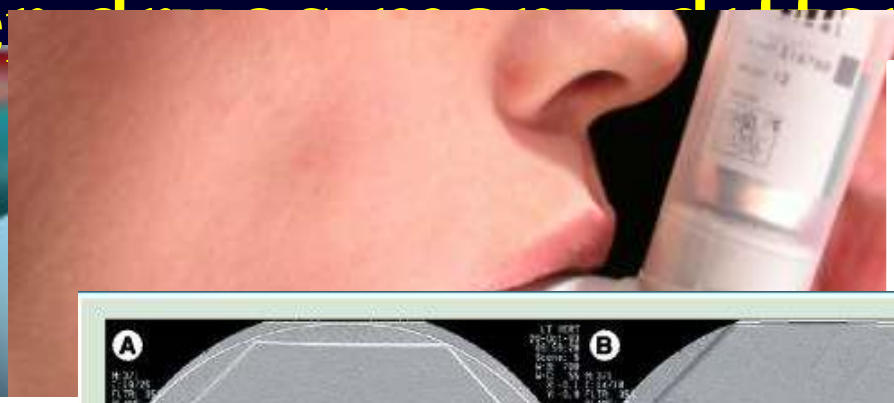
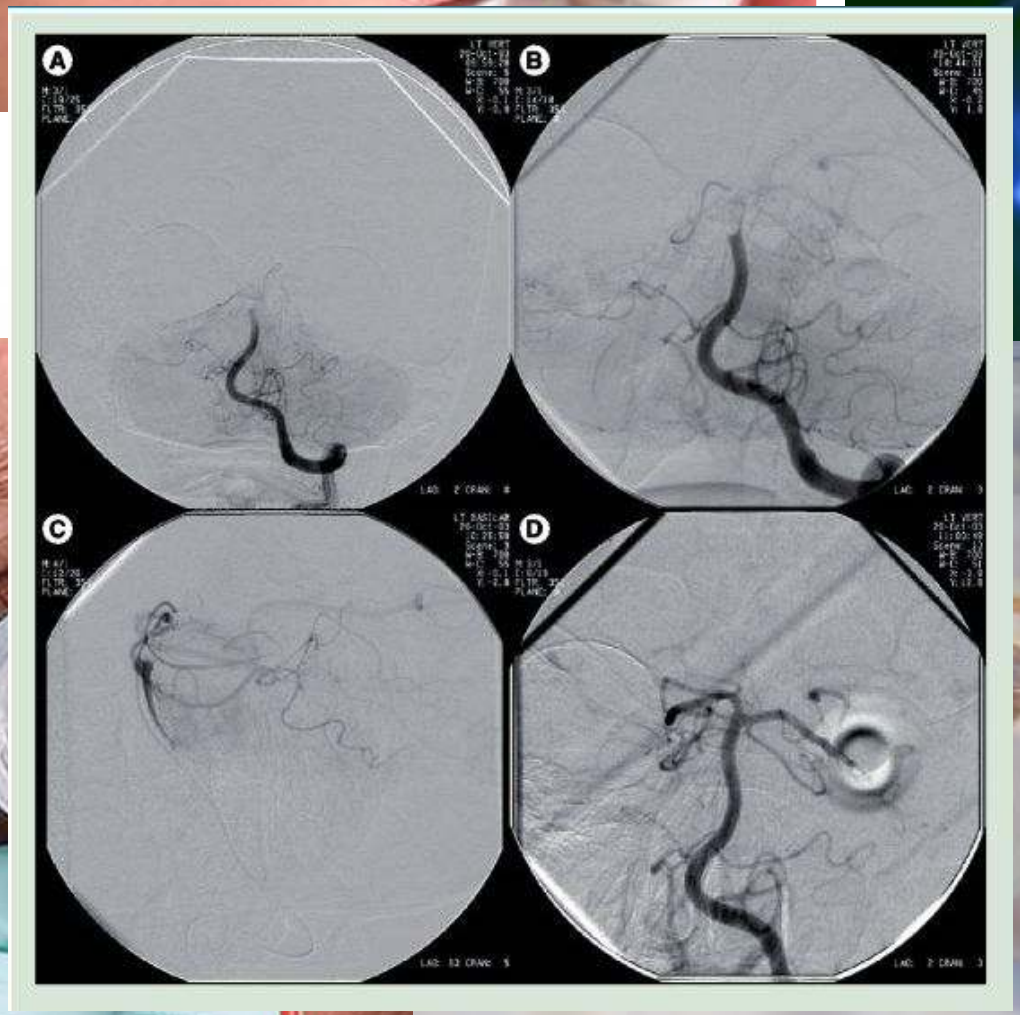
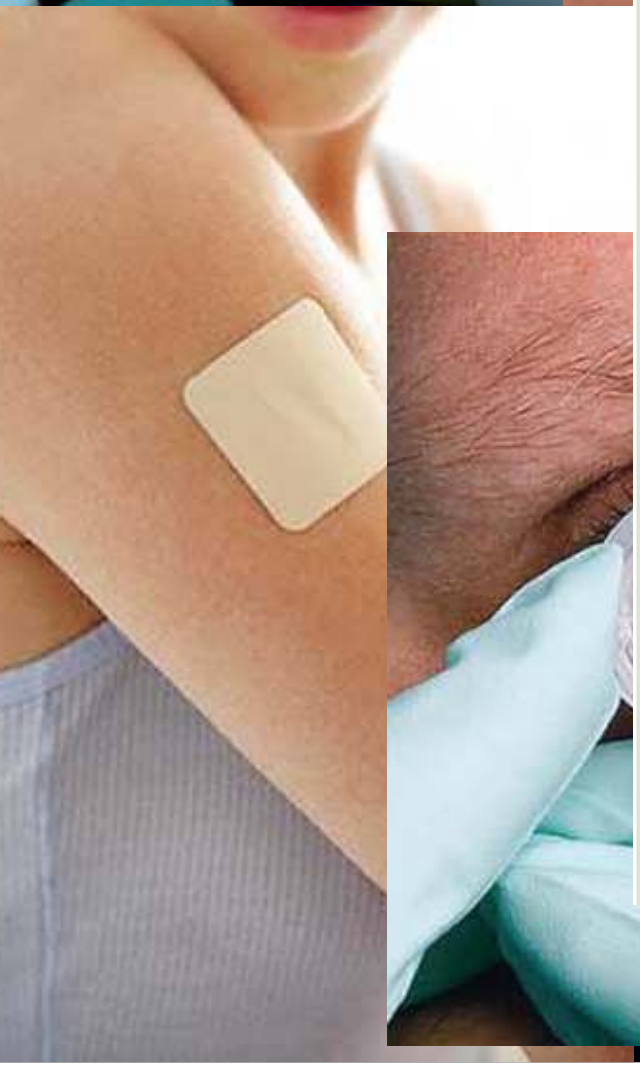
We deliver drugs many different ways:







Drug delivery can be:

- TOPICAL
- eye drops, teething medications, minoxidil (Rogaine)

- LOCAL
- local anesthetics, drug eluting stents, inhaled bronchodilators

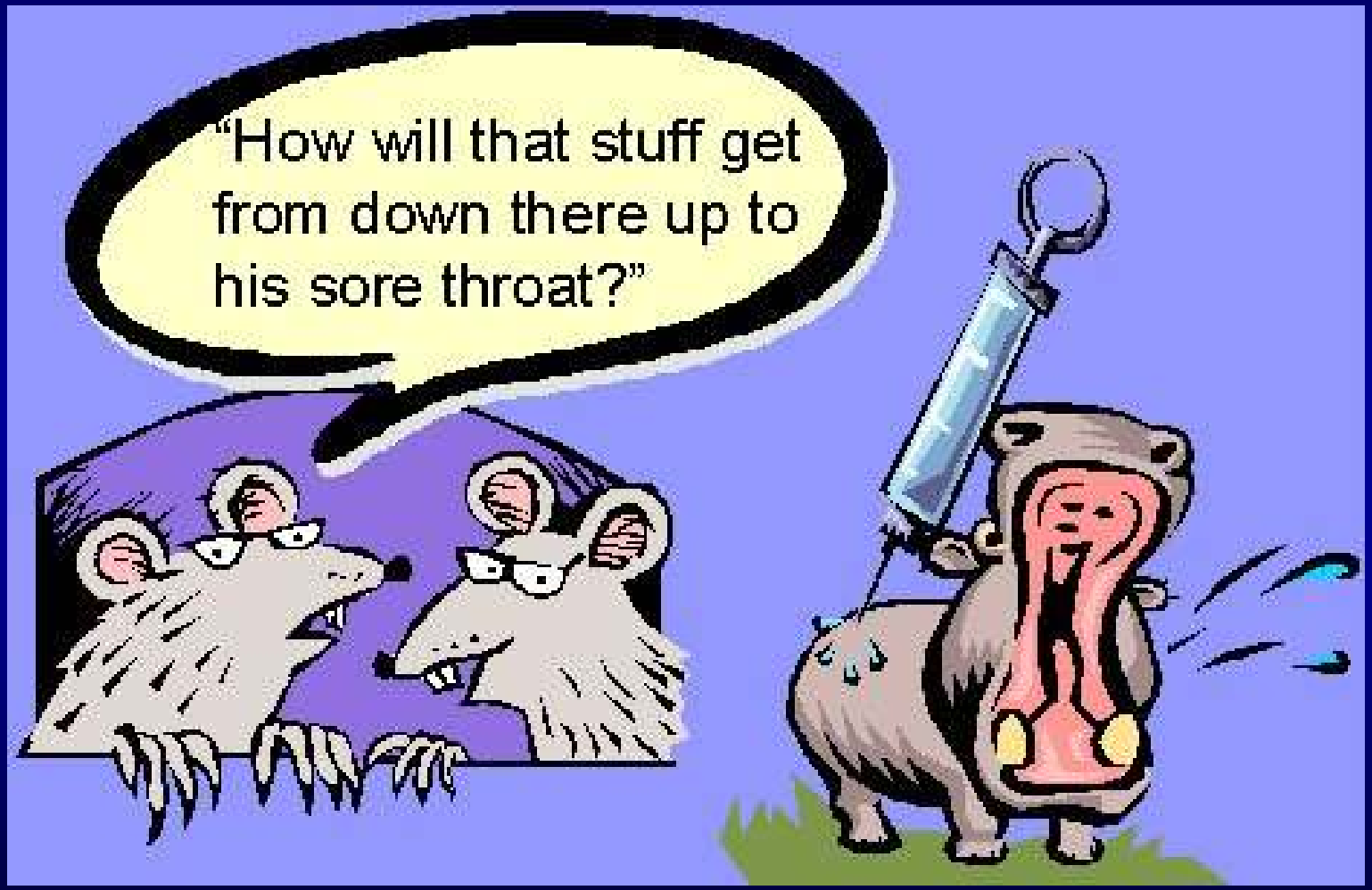
- REGIONAL
- isolated limb perfusion, light activated medications
-
- SYSTEMIC
- oral ingestion, intravenous administration

Drugs delivered via any route may:

- Disseminate systemically via circulatory transport
- Result in local or systemic toxicity
- Provoke immune responses
- Interact with other medications to potentiate or negate effects

We would like to see only very specific and titratable effects

Drugs may seem pretty smart…



But they need to be made smart by

- Proper formulation for the delivery environment
  - pH (e.g., local anesthetics)
  - size distribution (e.g., inhaled aerosols)
  - encapsulation for time release (e.g., “SR” oral meds)
- Chemical modification to avoid undesired responses
  - immune reactions
  - escape macrophages and RES
- Directing site-specificity

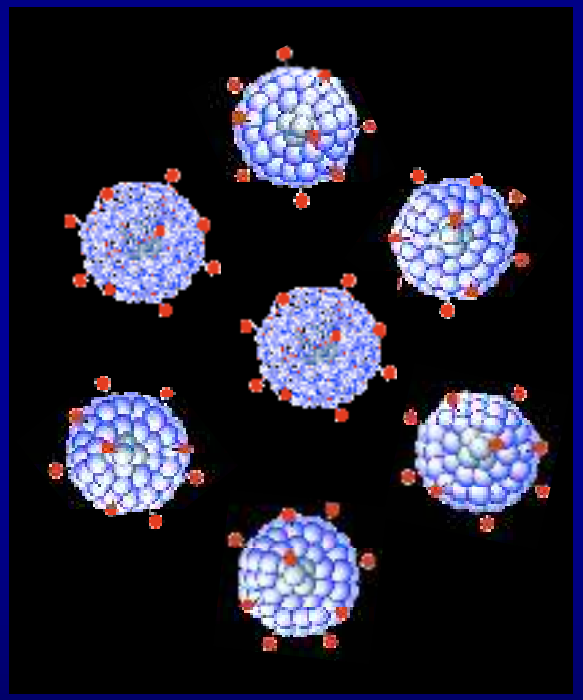
Site specificity: Creating magic bullets

What we want!

This means getting to a smaller length scale

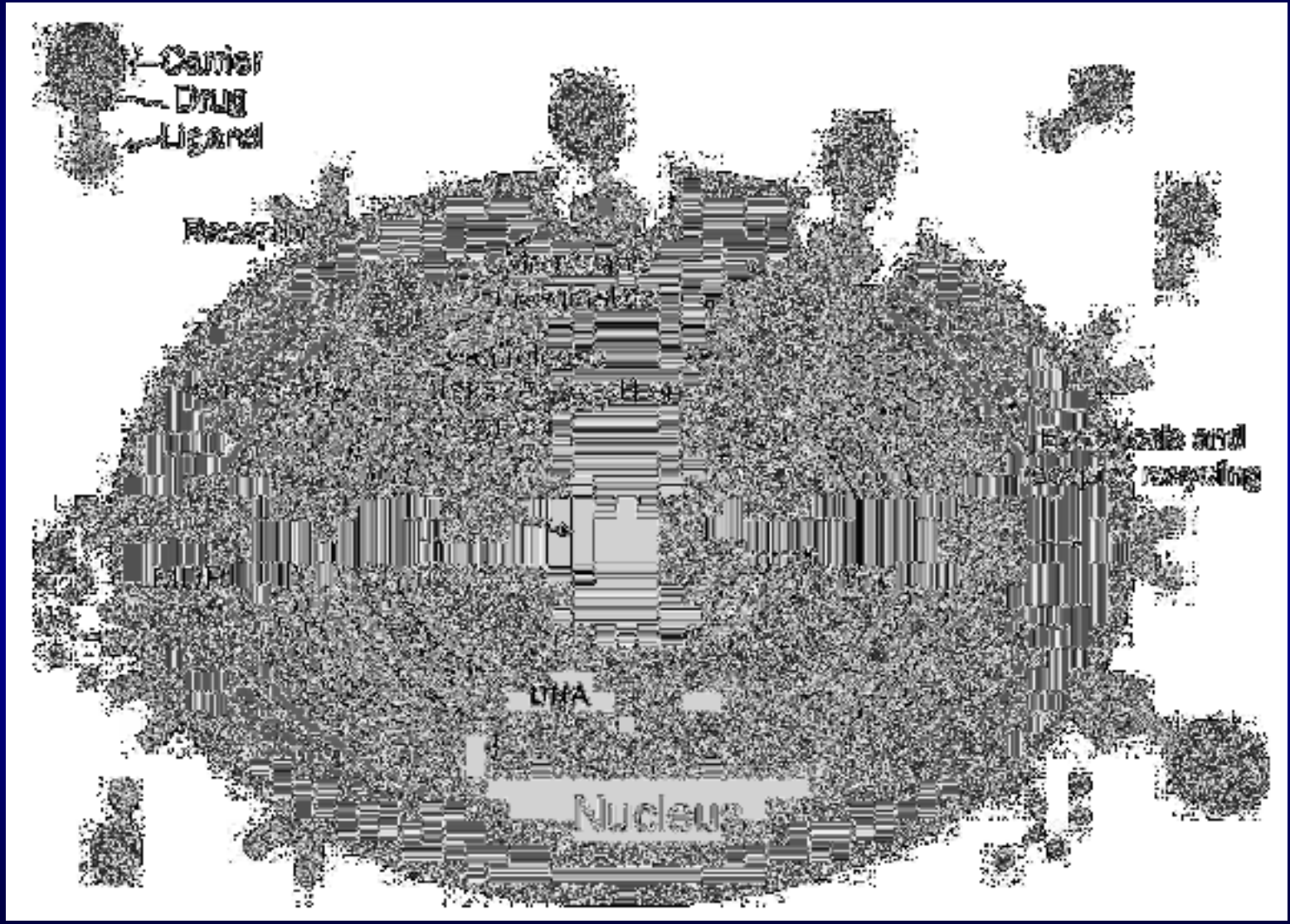
For drug targeting: nanoscale

Macro



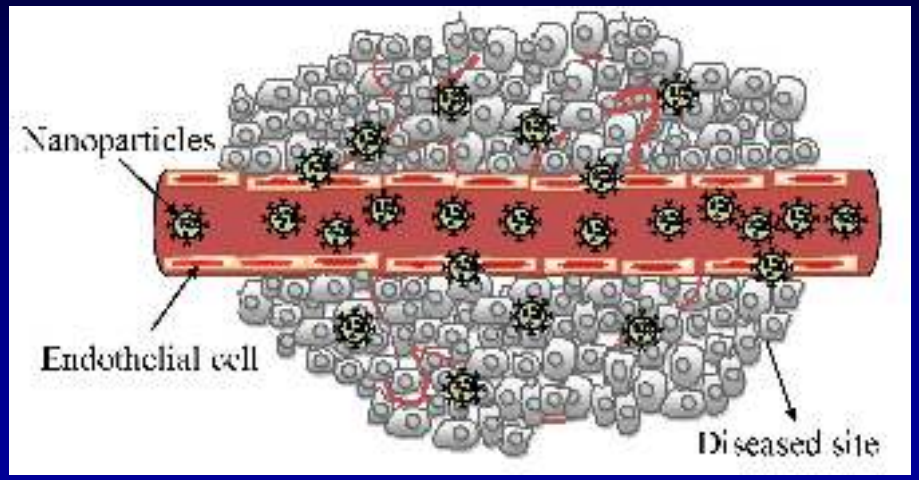
Nano

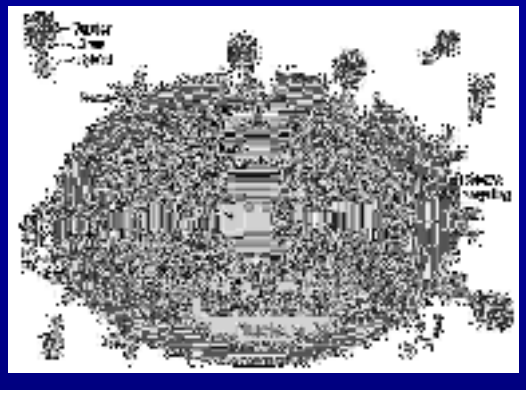
Simplified overview of TDD

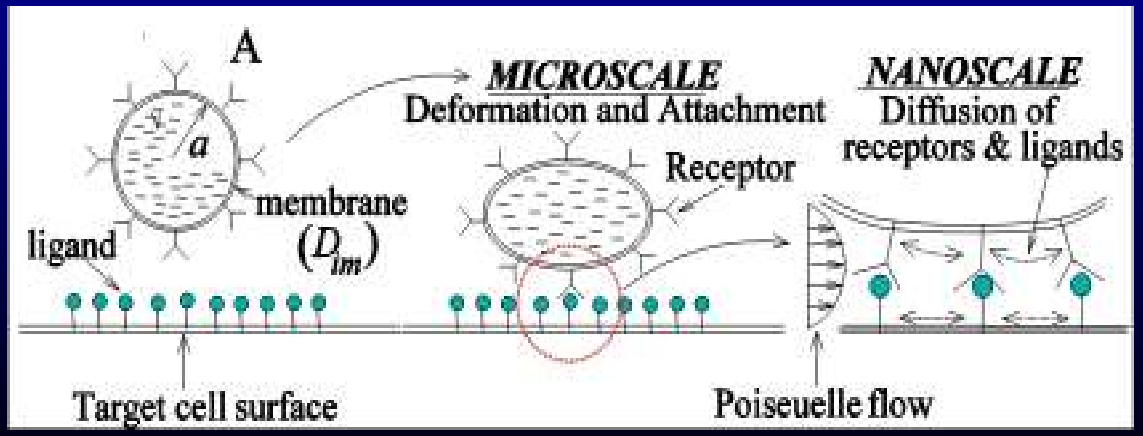


Clin Cancer Res 14: 1310-1316 (2008)

Drug packaging and targeting: Nano





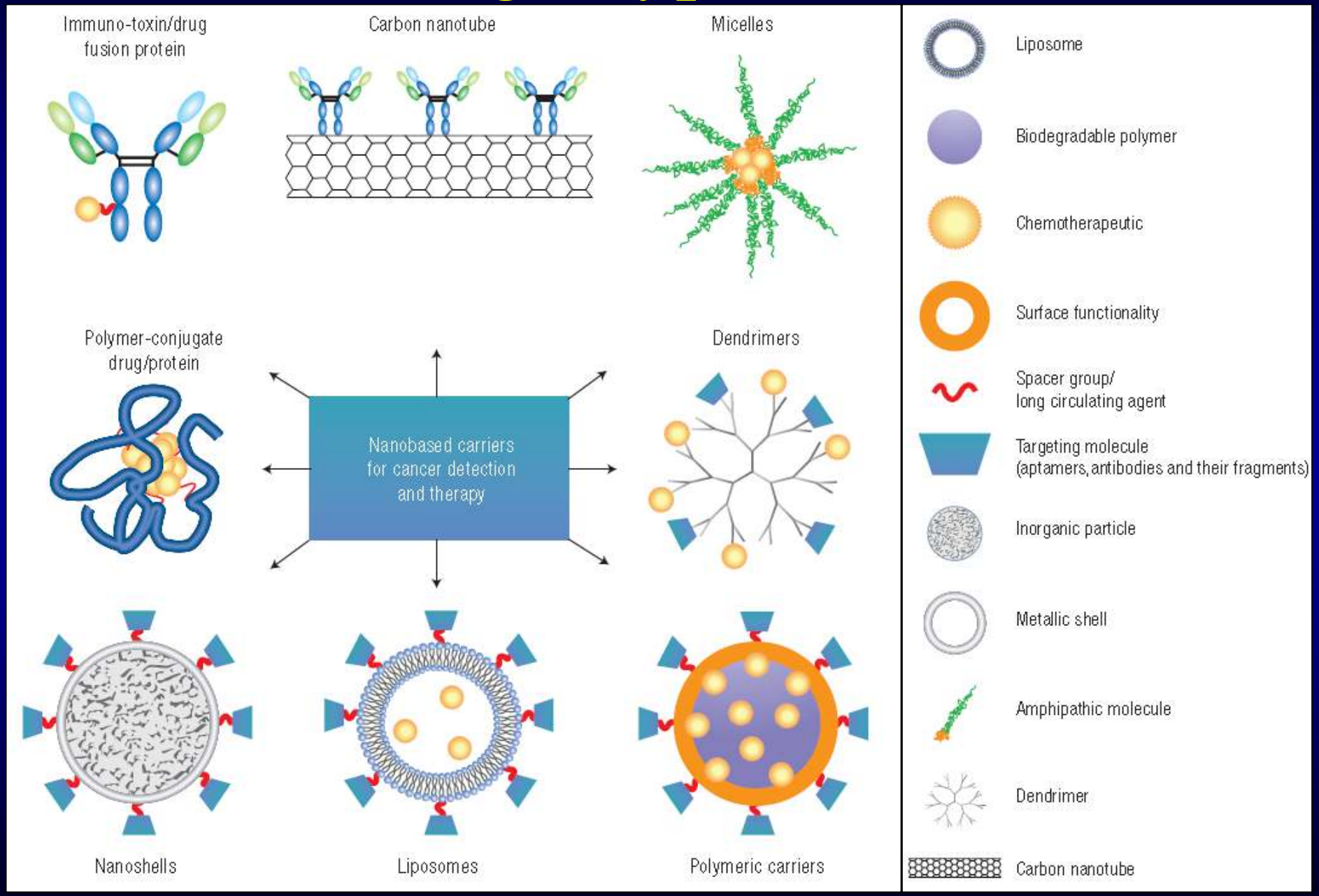


- Drug delivery by intravascular use of targeted nanocarriers holds promise for personalized medicine
- Clinical optimization of drug transport requires accurate description of carrier motion in the bloodstream and near endothelial cells
- Synergistic computational approach is essential to determining delivery: high throughput; complex motions; nanocarrier design specification; molecular events and membrane dynamics not accessible by imaging
- Hydrodynamic interactions and binding mechanics are important

Nano offers great potential, but also raises lots of questions

1. What are the right types of carriers?
2. What are the molecular targets?
3. What are the targeting molecules?
4. How are the carriers constructed and loaded (drug, targeting)?
5. How are the carriers administered?
6. How do carriers reach diseased tissues?
7. How are the carriers internalized and trafficked by cells?
8. How is the drug released from the carrier?
9. Is this more effective and/or less toxic?
10. How is any of this optimized?
11. More, more, more

What are the right types of carriers?



Nature Nanotechnology 2: 751-760 (2007)

What are the molecular targets?

Cell surface and ECM-docking receptors in tumor vessels

Receptor	References
RGD-directed integrins (αvβ3 and αvβ5)	Ruoslahti, 2002; Desgrosellier and Cheresh, 2010
Aminopeptidase N	Pasqualini et al., 2000
TEMs	Carson-Walter et al., 2001
Endosialin	Christian et al., 2001
Cell surface nucleolin	Christian et al., 2003
Cell surface annexin-1	Oh et al., 2004
Cell surface α32/gC1q receptor	Fogal et al., 2008
Cell surface galectin-1	Kenny et al., 2008
Fibronectin ED-B	Nilsson et al., 2001
Fibrin–fibronectin complexes	Pilch et al., 2006; Simberg et al., 2007
Interleukin-11 receptor α	Lewis et al., 2009
Protease-cleaved collagen IV	Xu et al., 2001; Mueller et al., 2009

What are the molecular targets?

1. Endothelial Cell Markers (*inflammatory*)
   a. ICAM-1
   b. PECAM
   c. Other (*integrins*?)

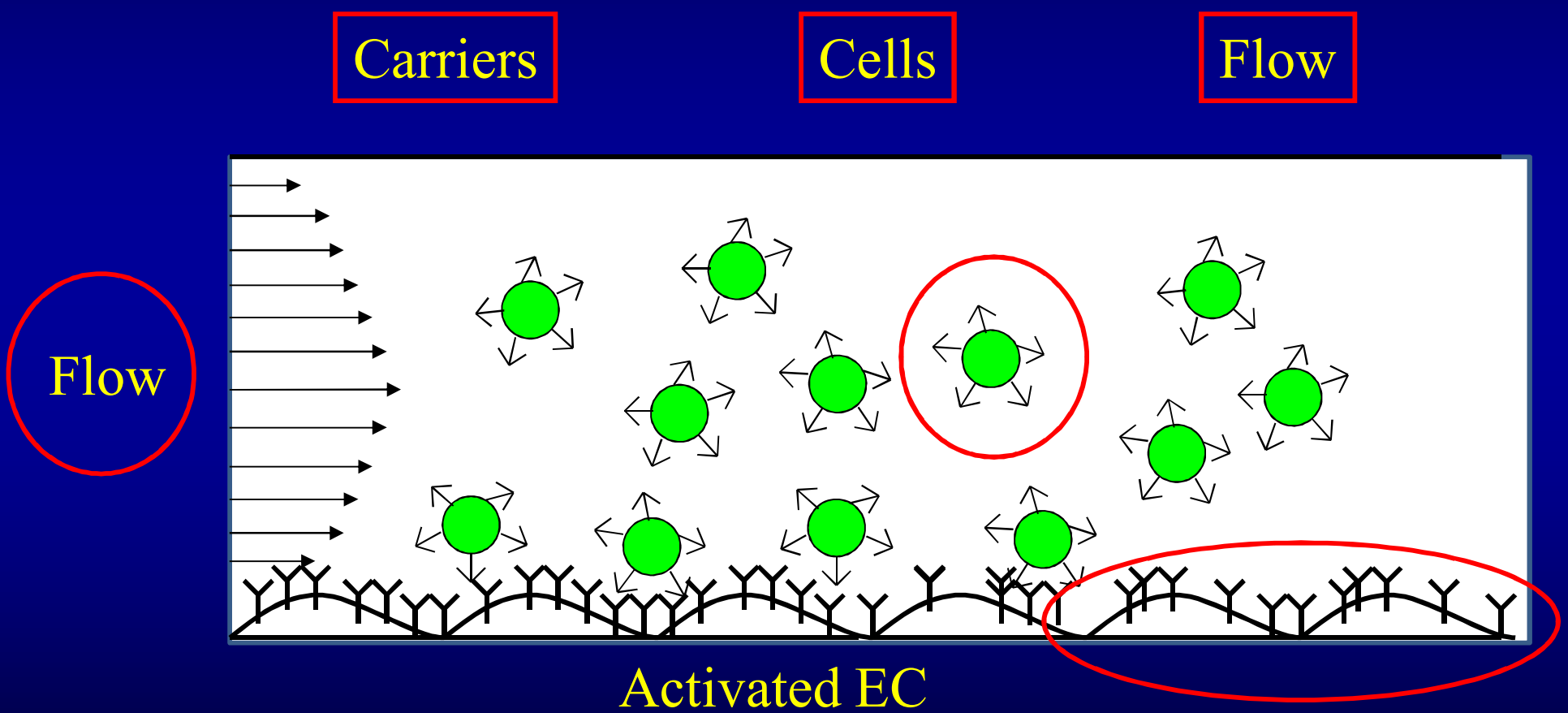
"Vascular*"
Hydrodynamic Considerations

*Our targets in ALI, I/R

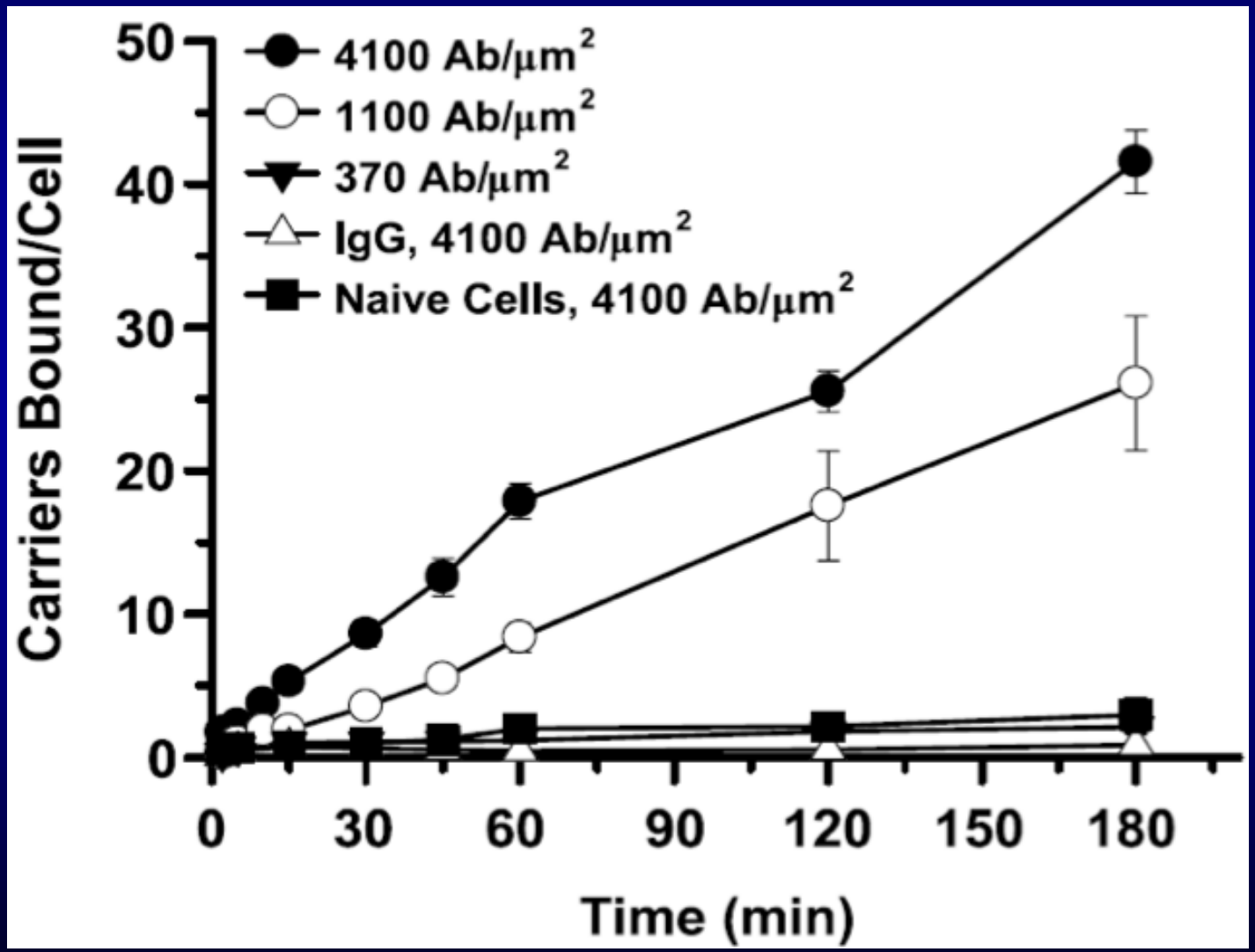
2. Tumor Cell Markers
   a. Breast
   b. Colorectal
   c. Prostate
   d. Hepatocellular
   e. Other

"Non -vascular"
Other important considerations

Basic Experimental Model: Control



Effects of Targeting Molecule Density and Time on Cellular Binding of Particles



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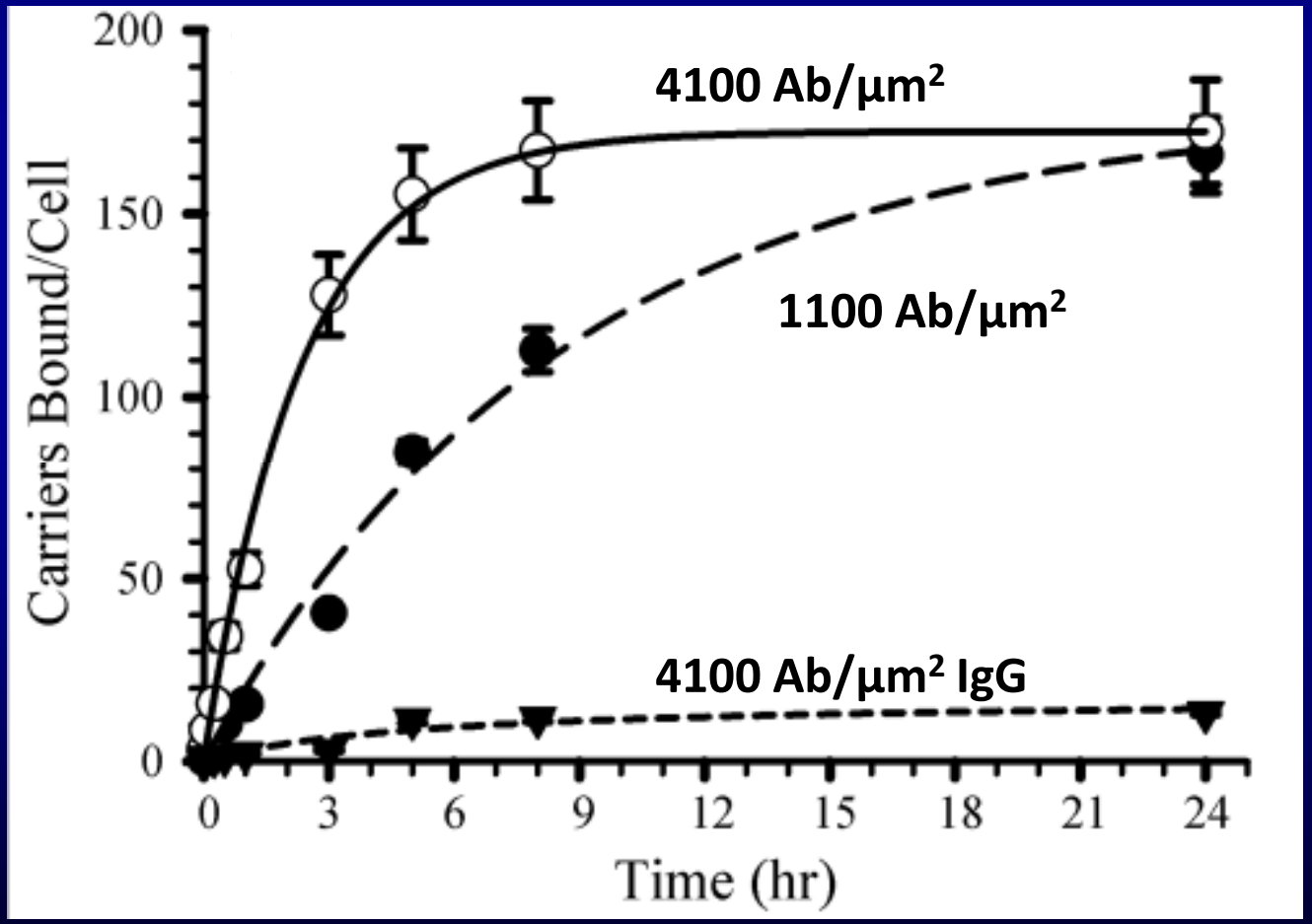
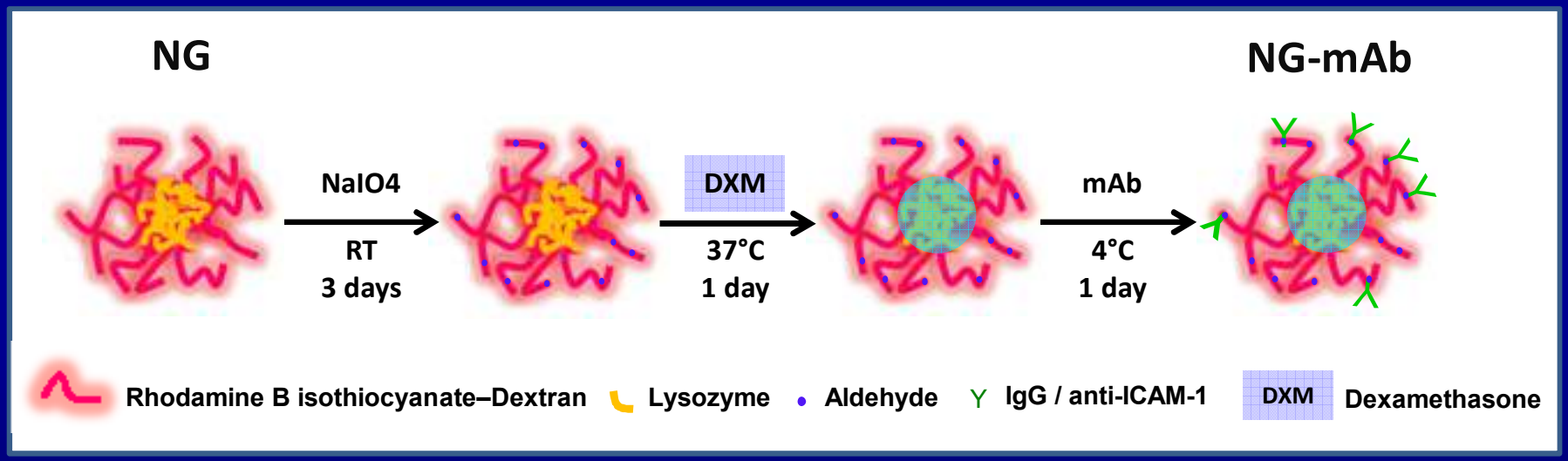
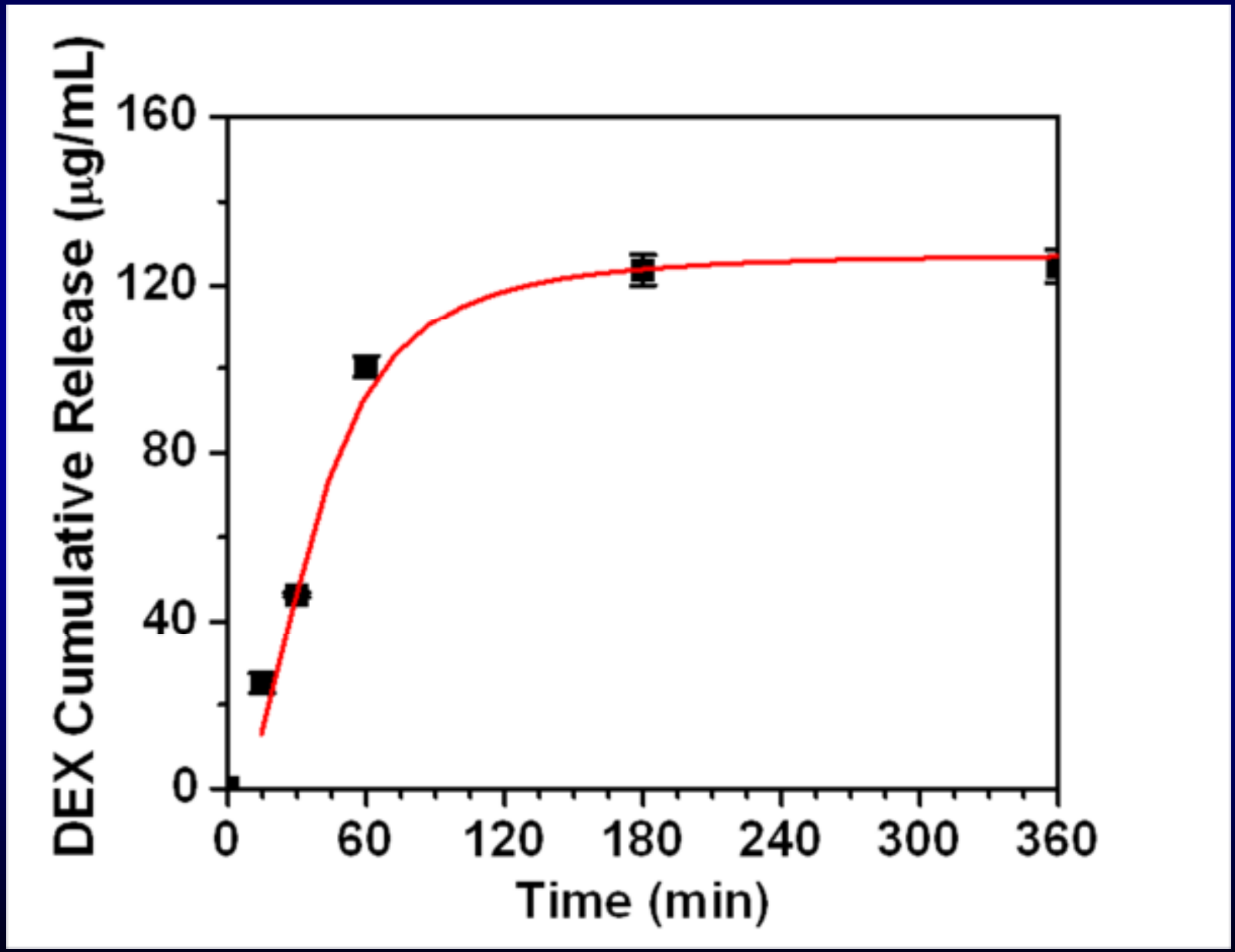


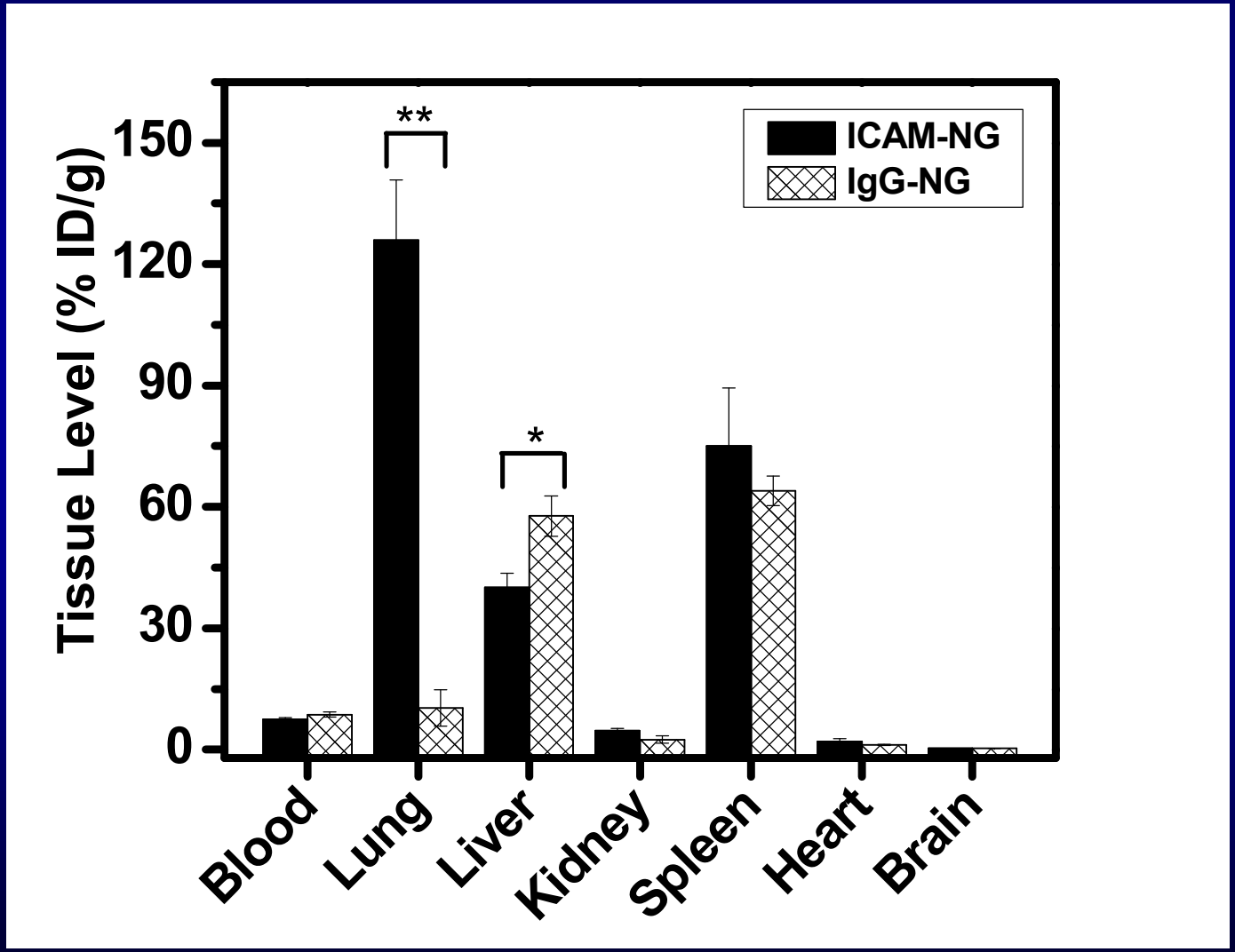
Synthesis of antibody-decorated nanogels



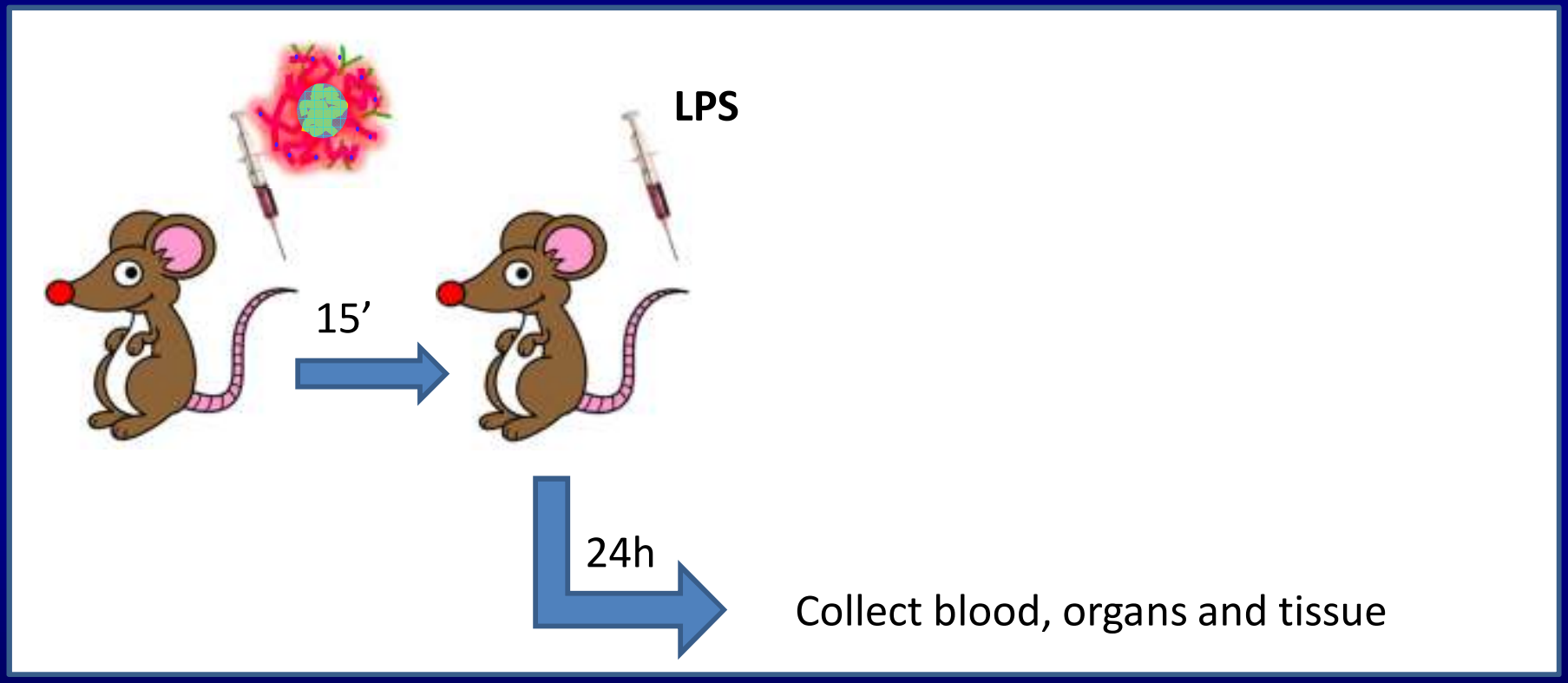
Drug carried in nanogel is releasable



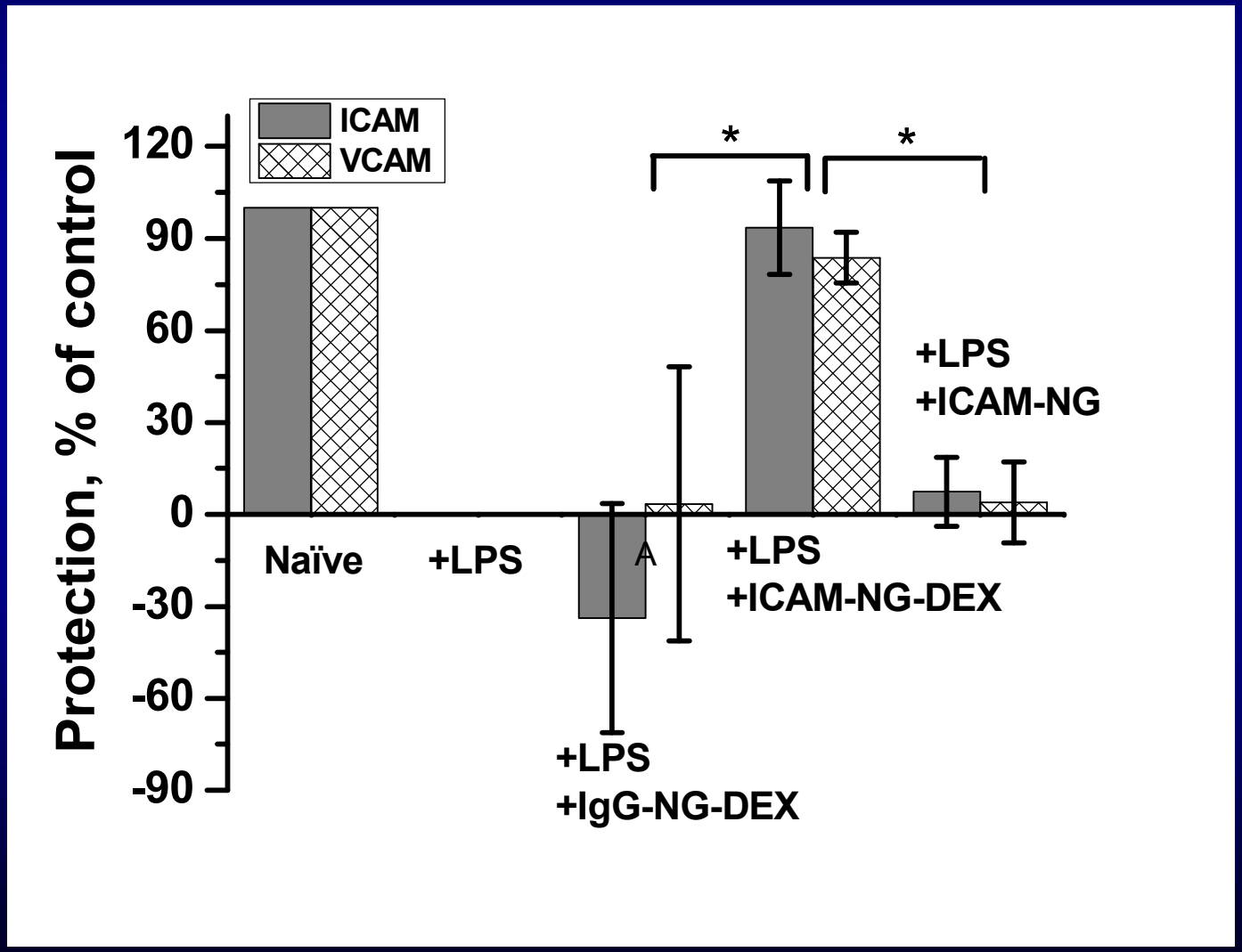
Biodistribution of targeted nanogels: Lung is targeted!



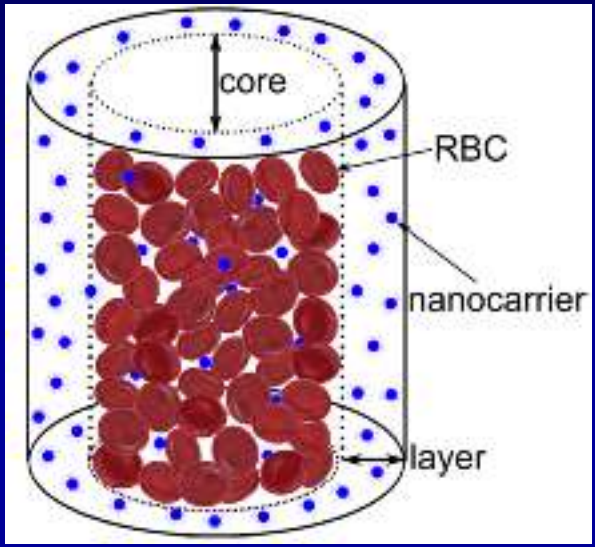
In vivo targeting of NG-mAb loaded with DXM via ICAM-1

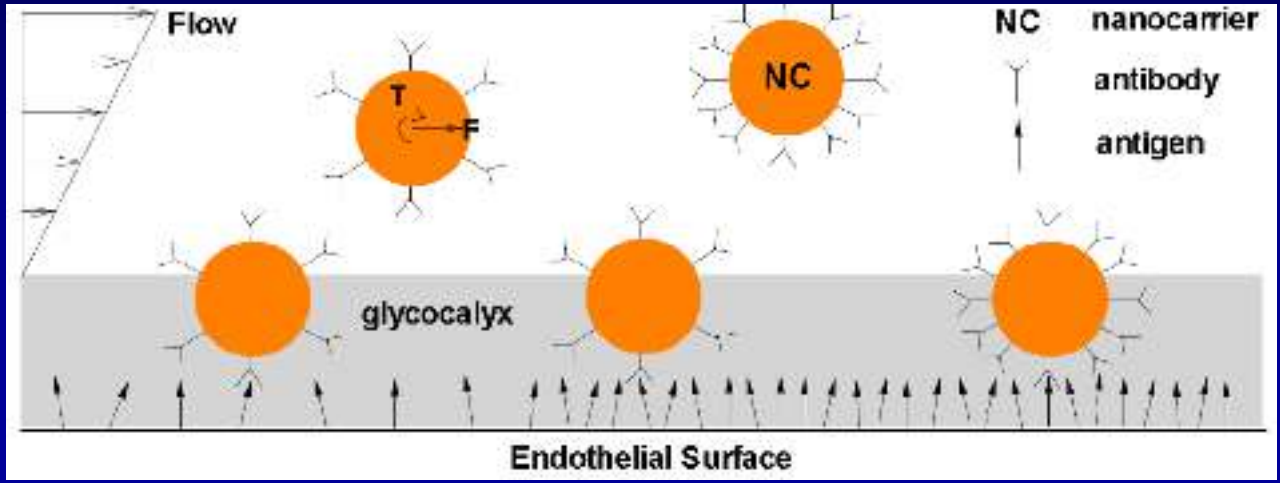


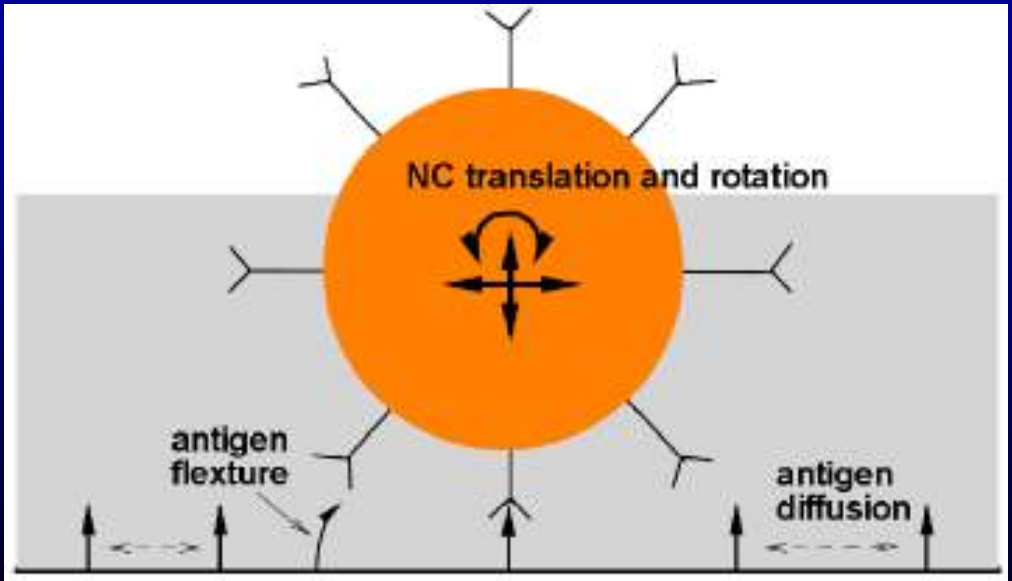
Biological Protection from LPS-induced Injury/Inflammation is Achieved

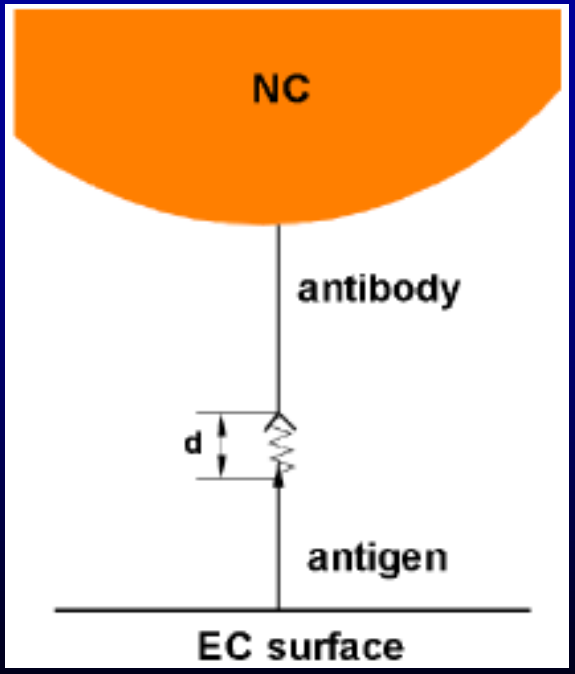


Hydrodynamic interactions and binding









Lingering questions about magic bullets

1. How does drug delivery get optimized?
   a. Carrier size, shape, type
   b. Carrier concentration in bulk
   c. How much to infuse
   d. Surface density of target molecule, linker
   e. Where/what is the drug

2. Is this more effective and/or less toxic?
   a. Evidence is scant at present
   b. Toxicity of carrier vs drug
   c. What studies should be done first?

NEXT