Biologic Barriers to In Vivo Nanomedicine Delivery: Major Hurdles for Clinical Translation

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LEADING MEDICINE℠

The Promise of Nanomedicine for In Vivo Diagnosis and Therapy

CONTROL

Ideal Therapy

- Precise Targeting (Tissue/Cell/Molecular)
- Precise Action (Maximize therapeutic action and minimize toxicity and side effects)
- Precise Timing (On when it is needed, Off when it is not needed)

Implicit in these design goals is the requirement for precise control mechanisms that can either respond to local environments automatically or respond to signals sent remotely.

Characteristics of an ideal tumour-targeted nanomedicine

(1) Increase drug localisation in the tumour through:

(a) Passive targeting

(b) Active targeting

(2) Decrease drug localisation in sensitive, non-target tissues

(3) Ensure minimal drug leakage during transit to target

(4) Protect the drug from degradation and from premature clearance

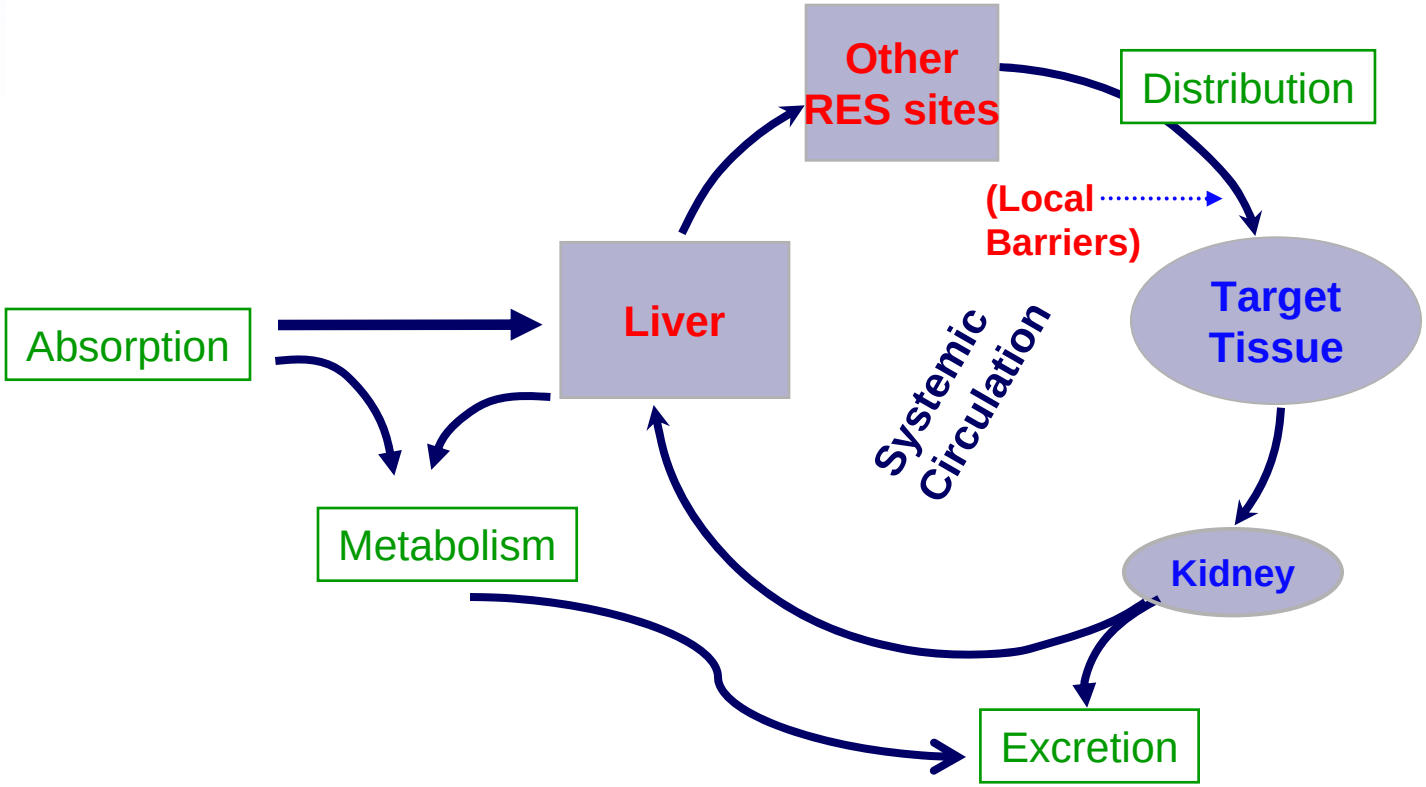
(5) Retain the drug at the target site for the desired period of time

(6) Facilitate cellular uptake and intracellular trafficking

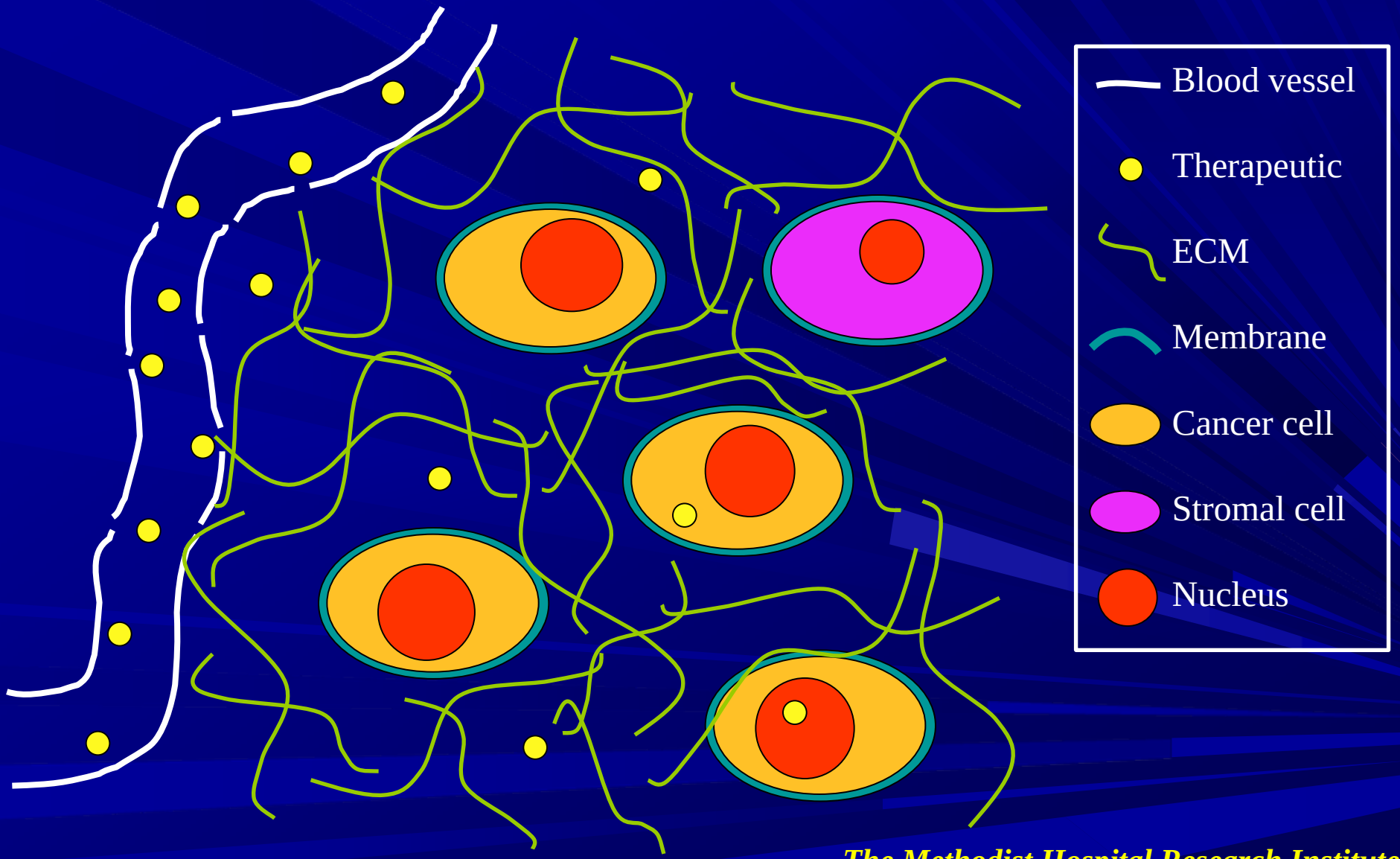
(7) Biocompatible and biodegradable

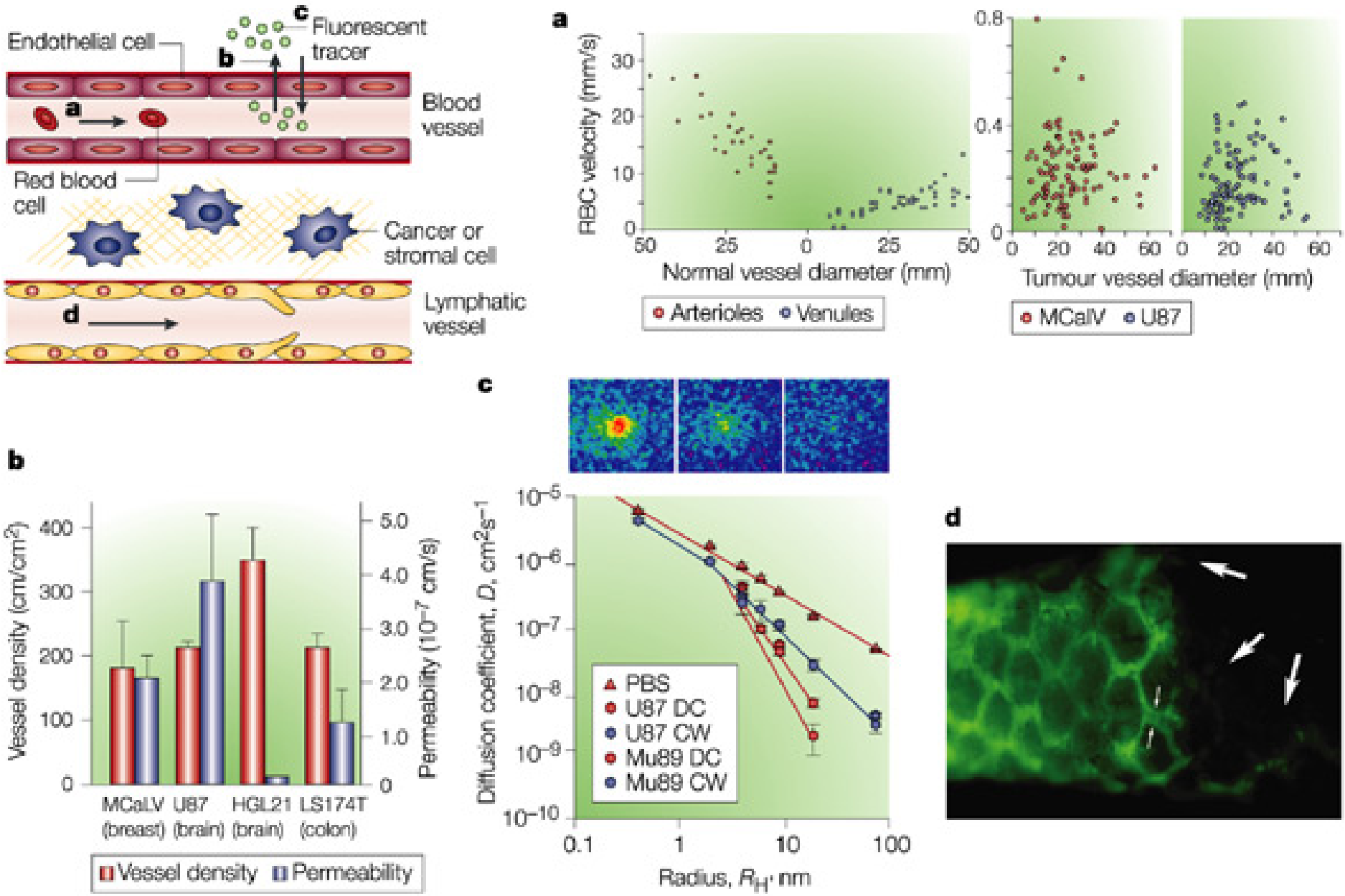
Lammers T, et al. British Journal of Cancer 2008;99:392-397.

Pharmacokinetics; ADME



Local Transport barriers

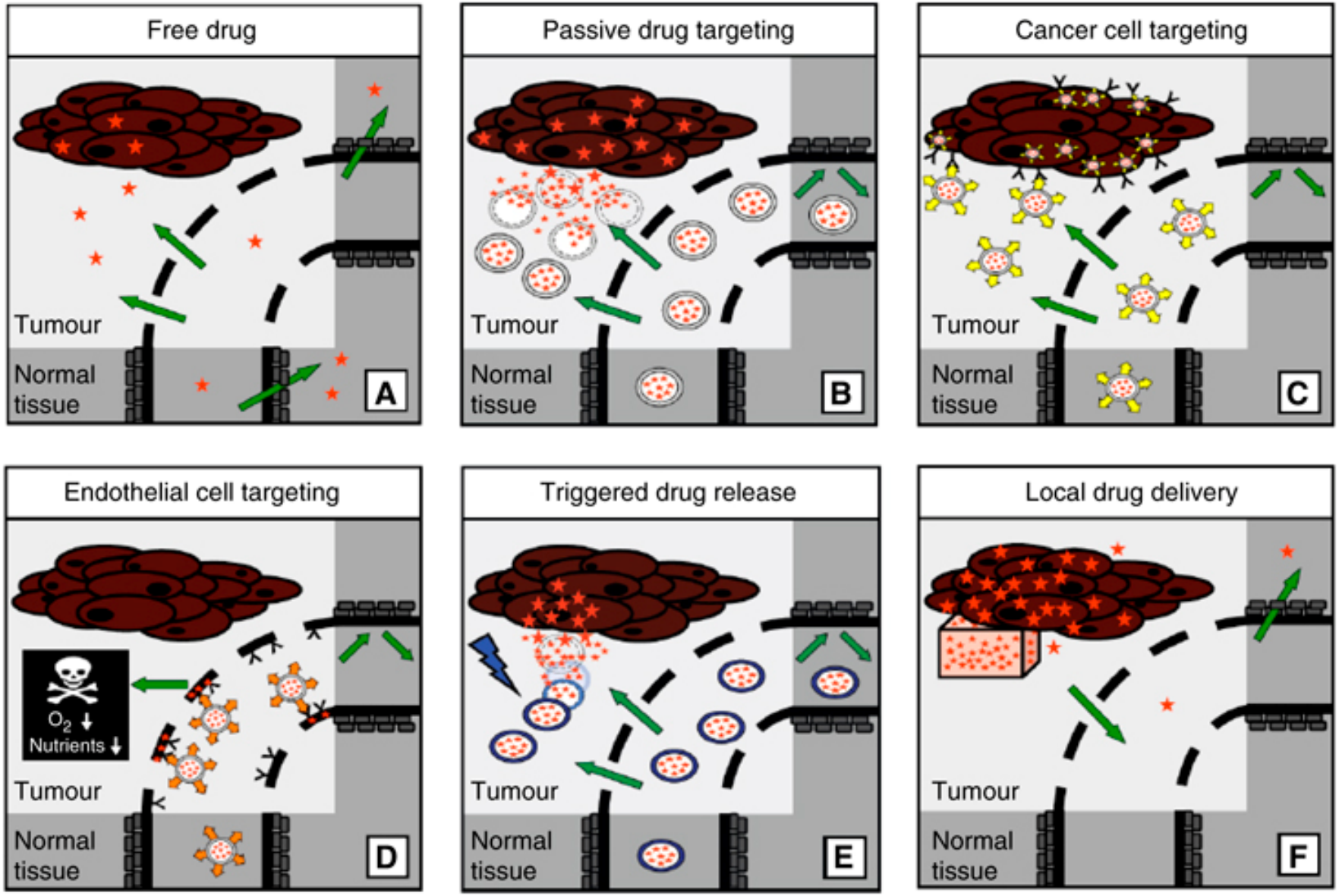




Nature Reviews | Cancer

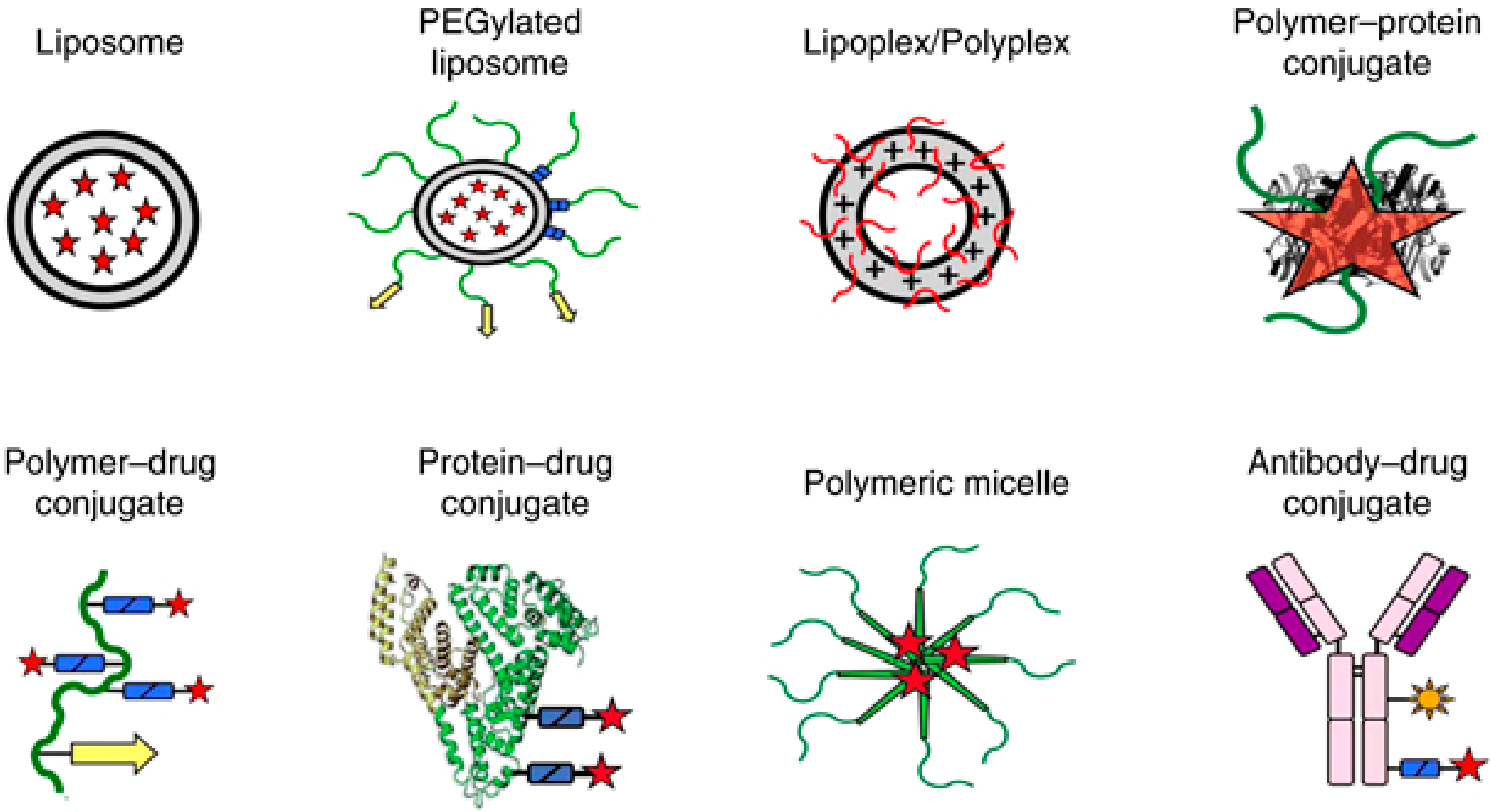
Jain RK, et al. Nature Reviews 2002;2:266-276

Clinically Utilized Drug Targeting Strategies



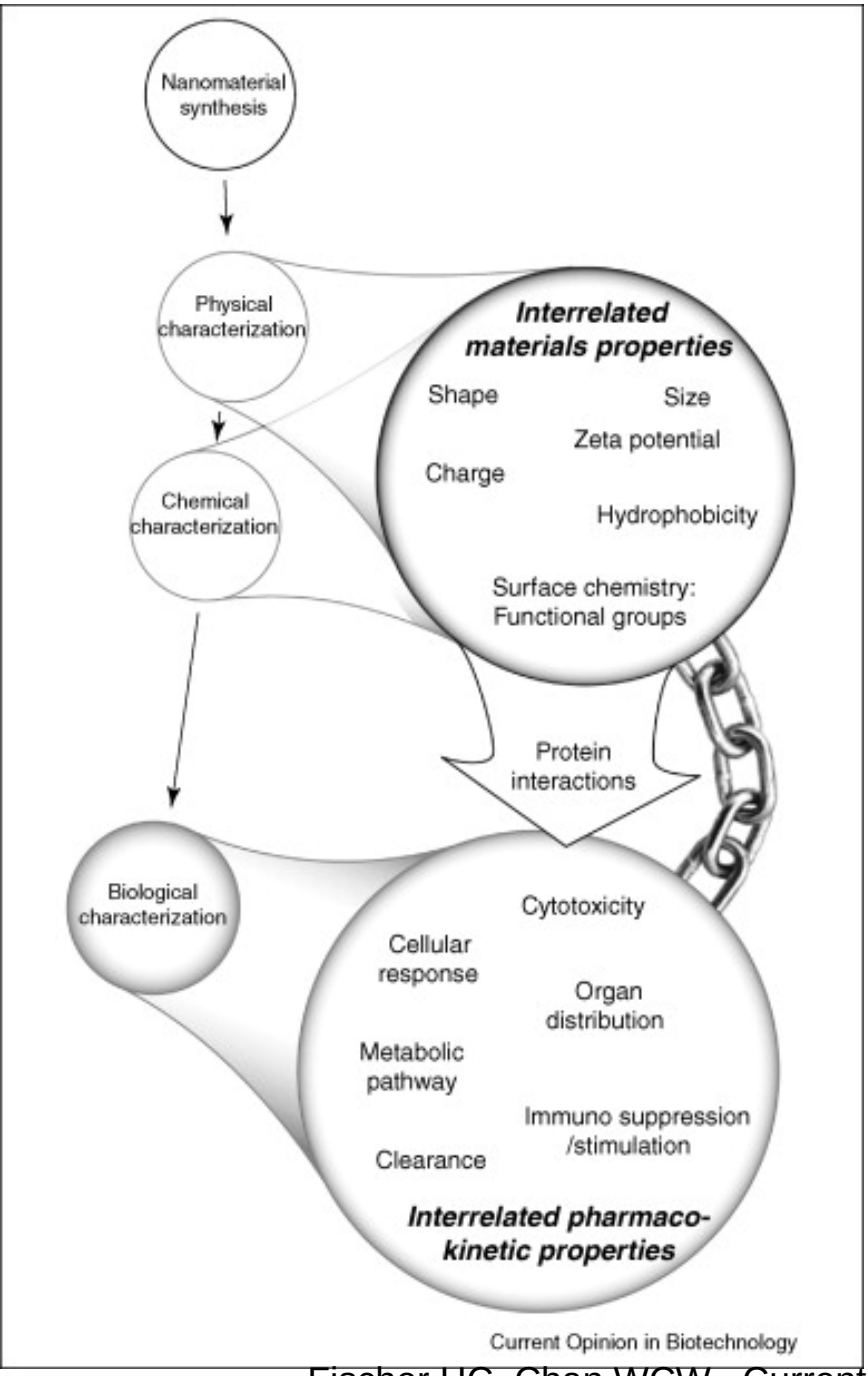
Lammers T, et al. British Journal of Cancer 2008;99:392-397.

Examples of Clinically Used Tumor-targeted Nanomedicines



Lammers T, et al. British Journal of Cancer 2008;99:392-397.

Compound	Name	Indication	Status
Liposomal doxorubicin	Myocet, Caelyx (Doxil)	Breast, ovarian, KS	Approved
Liposomal daunorubicin	Daunoxome	Kaposi sarcoma	Approved
Liposomal vincristine	Onco-TCS	Non-hodgkin lymphoma	Approved
Liposomal cisplatin	SPI-77	Lung	Phase II
Liposomal lurtotecan	OSI-221	Ovarian	Phase II
Cationic liposomal c-Raf AON	LErafAON	Various	Phase I/II
Cationic liposomal E1A pDNA	PLD-E1A	Breast, ovarian	Phase I/II
Thermosensitive liposomal doxorubicin	ThermoDox	Breast, liver	Phase I
Albumin-paclitaxel	Abraxane	Breast	Approved
Albumin-methotrexate	MTX-HSA	Kidney	Phase II
Dextran-doxorubicin	DOX-OXD	Various	Phase I
PEG-L-asparaginase	Oncaspar	Leukaemia	Approved
PEG-IFN2a/-IFN2b	PegAsys/PegIntron	Melanoma, leukaemia	Phase I/II
PHPMA-doxorubicin	PK1	Breast, lung, colon	Phase II
Galactosamine-targeted PK1	PK2	Liver	Phase I/II
PGA-paclitaxel	Xyotax	Lung, ovarian	Phase III
Paclitaxel-containing polymeric micelles	Genexol-PM	Breast, lung	Phase II
Cisplatin-containing polymeric micelles	Nanoplatin	Various	Phase I
Doxorubicin-containing polymeric micelles	NK911	Various	Phase I
SN38-containing polymeric micelles	LE-SN38	Colon, colorectal	Phase I
^{90}Yttrium-Ibritumomab tiuxetan (alpha-CD20)	Zevalin	Non-hodgkin lymphoma	Approved
DTA-IL2 fusion protein (alpha-CD25)	Ontak	T-cell lymphoma	Approved
Ozogamycin-gemtuzumab (alpha-CD33)	Mylotarg	Leukaemia	Approved
Doxorubicin-cBR96 (alpha-CD174)	SGN-15	Lung, prostate, breast	Phase II



Special ADME Considerations for Nanmedicine

- One cannot predict in vivo biodistribution based on nanostructure physical and chemical properties.
- Nanostructures can distribute to various organs intact, modified or metabolized.
- Nanostructures can enter the cells of various organs (e.g. RES) and reside in them for an unknown amount of time before moving to other organs or excreted.
- Unique routes of exposure will dictate specific fate of the nanostructures (e.g. inhalation, dermal exposures, etc.)
- Binding kinetics between nanostructures and protein(s) not well known.
- How different components of nanostructures are metabolically processed and excreted not fully known.

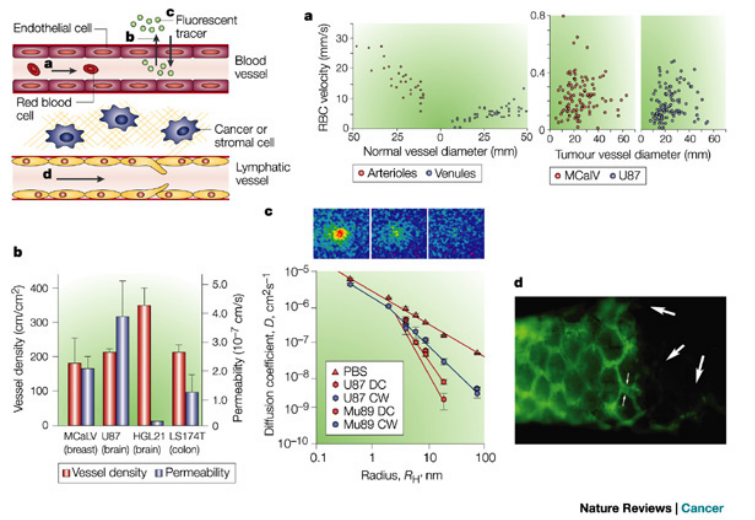
Fischer HC, Chan WCW. Current Opinion in Biotechnology 2007;18:565-571.

Survey of prevalent nanostructure classes, applications, concerns and areas of interest

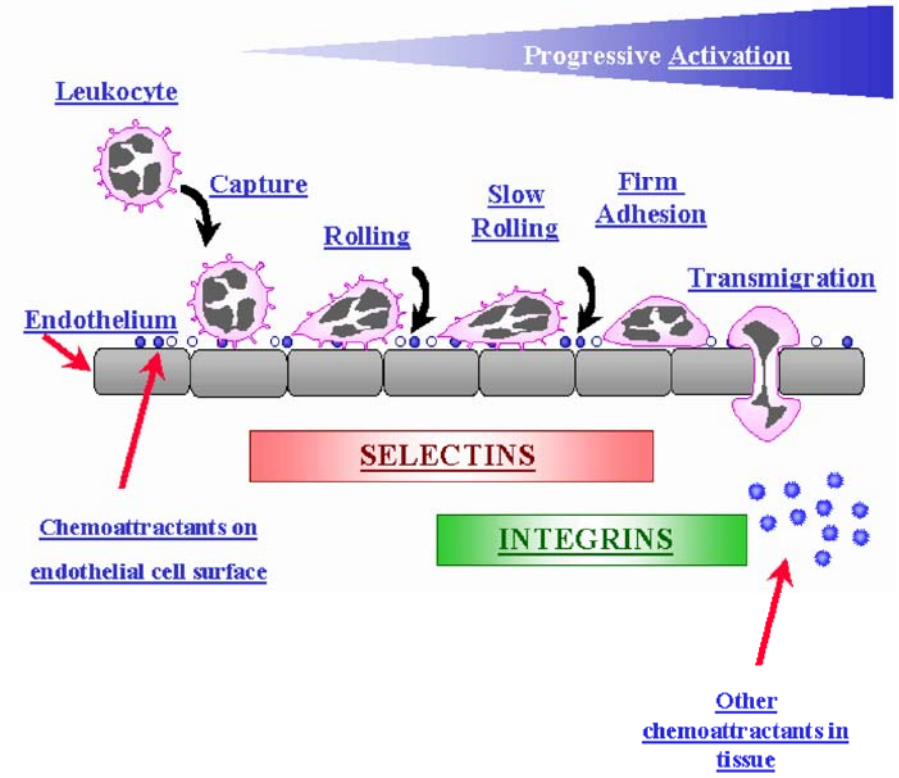
Nanostructure	Application (example)	Concerns	Mechanistic areas of interest
Metal nanoparticles	Contrast agents; drug delivery	Element specific toxicity; reactive oxygen species	Excretion
Nanoshells	Hyperthermia therapy	None demonstrated	Excretion
Fullerenes	Vaccine adjuncts; hyperthermia therapy	Antibody generation	Immunotoxicity
Quantum dots	Fluorescent contrast agent	Metabolism	Intracellular/ organ redistribution; excretion
Polymer nanoparticles	Drug delivery; therapeutics	Unknown	Metabolism; immunotoxicity; complement activation
Dendrimer	Guest delivery of drug/radiolabel dose	Metabolic path	Surface chemistry and elemental effects; complement activation
Liposome	Drug delivery; contrast agent vehicle	Hypersensitivity reactions	Complement activation

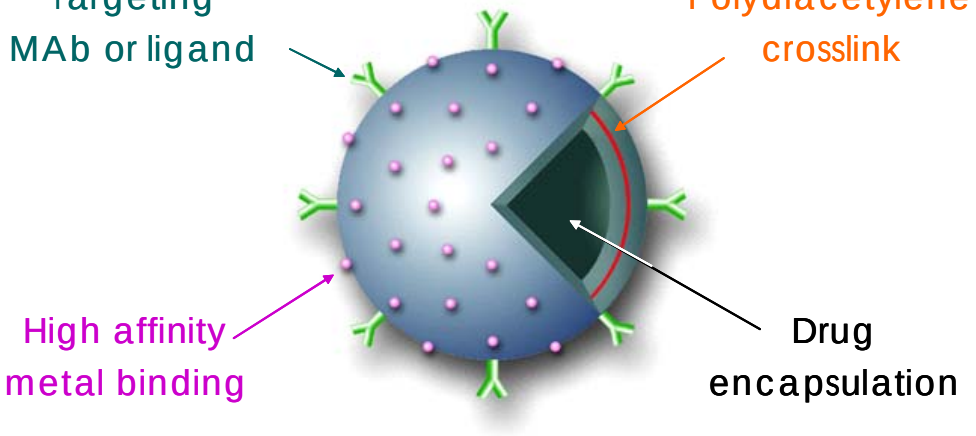
Fischer HC, Chan WCW. Current Opinion in Biotechnology 2007;18:565-571.

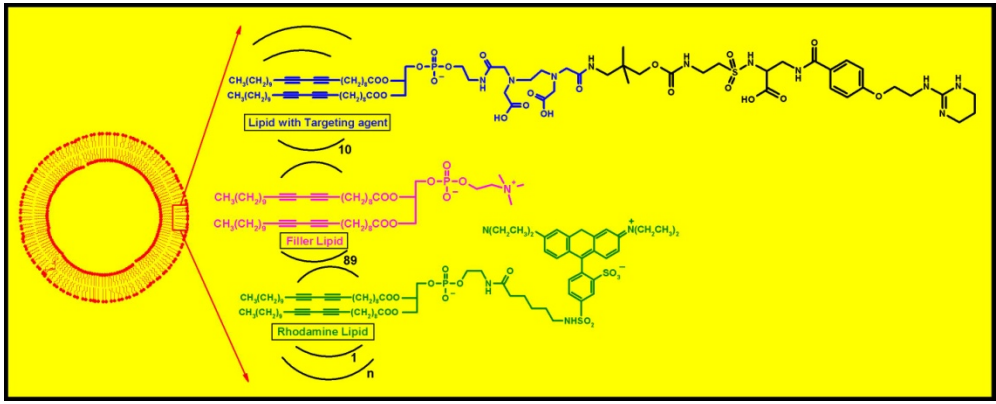
A Nanoscale Targeted PV



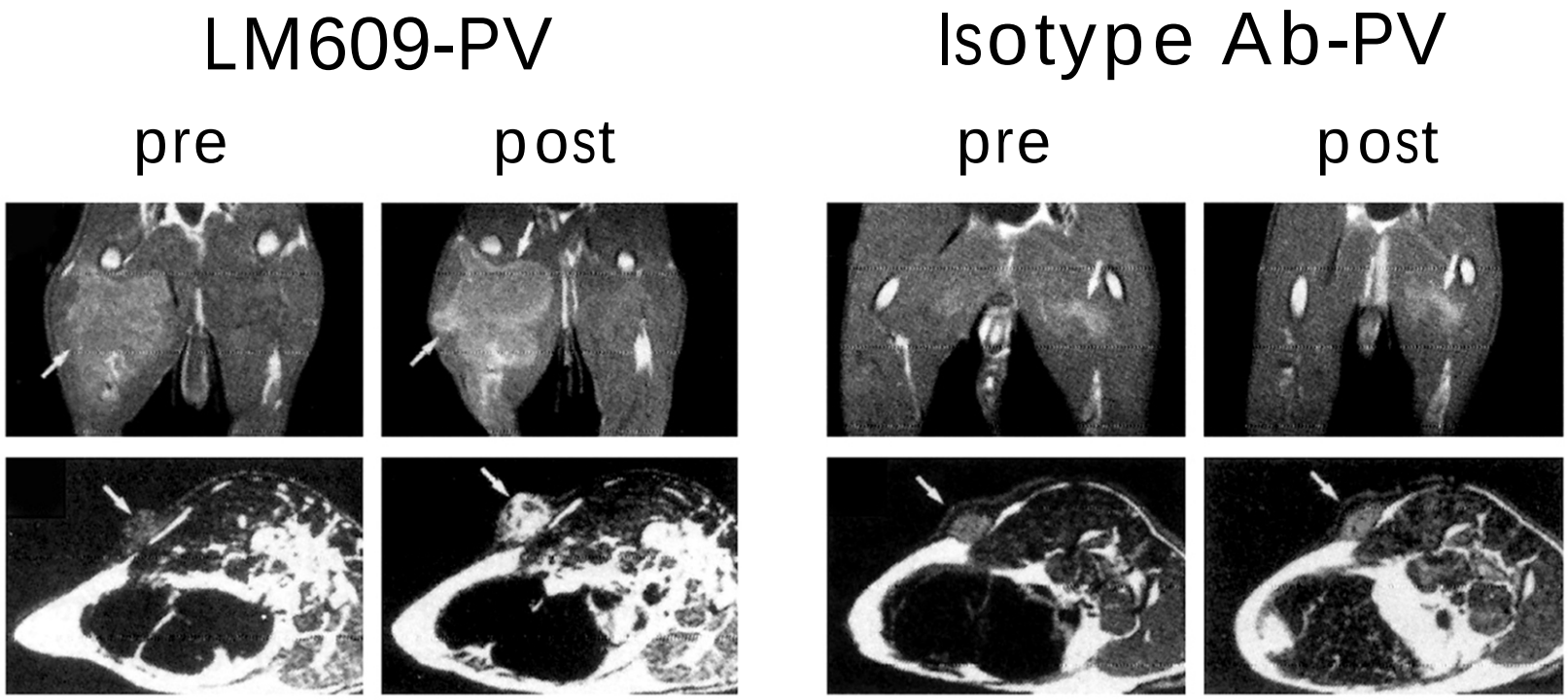
Jain RK, et al. Nature Reviews 2002;2:266-276







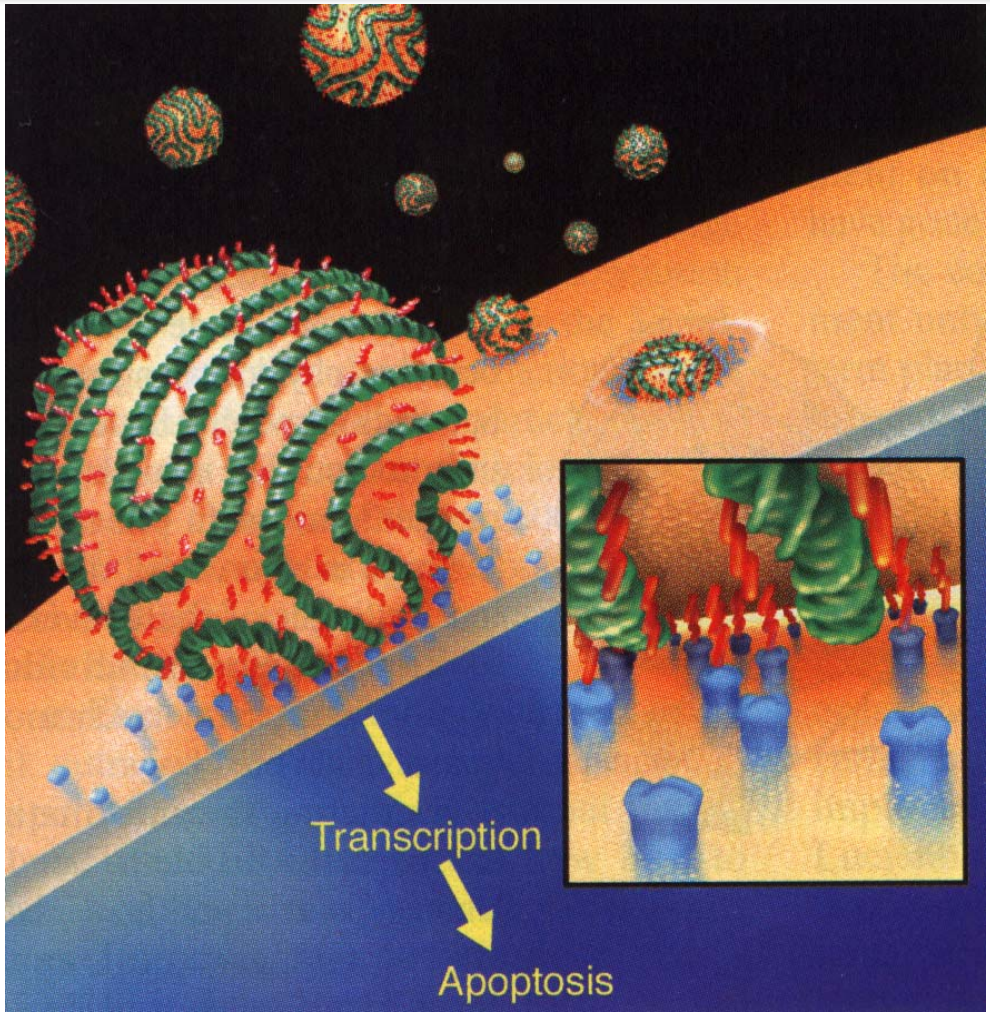
Molecular Imaging of Angiogenesis



T1w MRI images: Vx2 carcinoma rabbit model

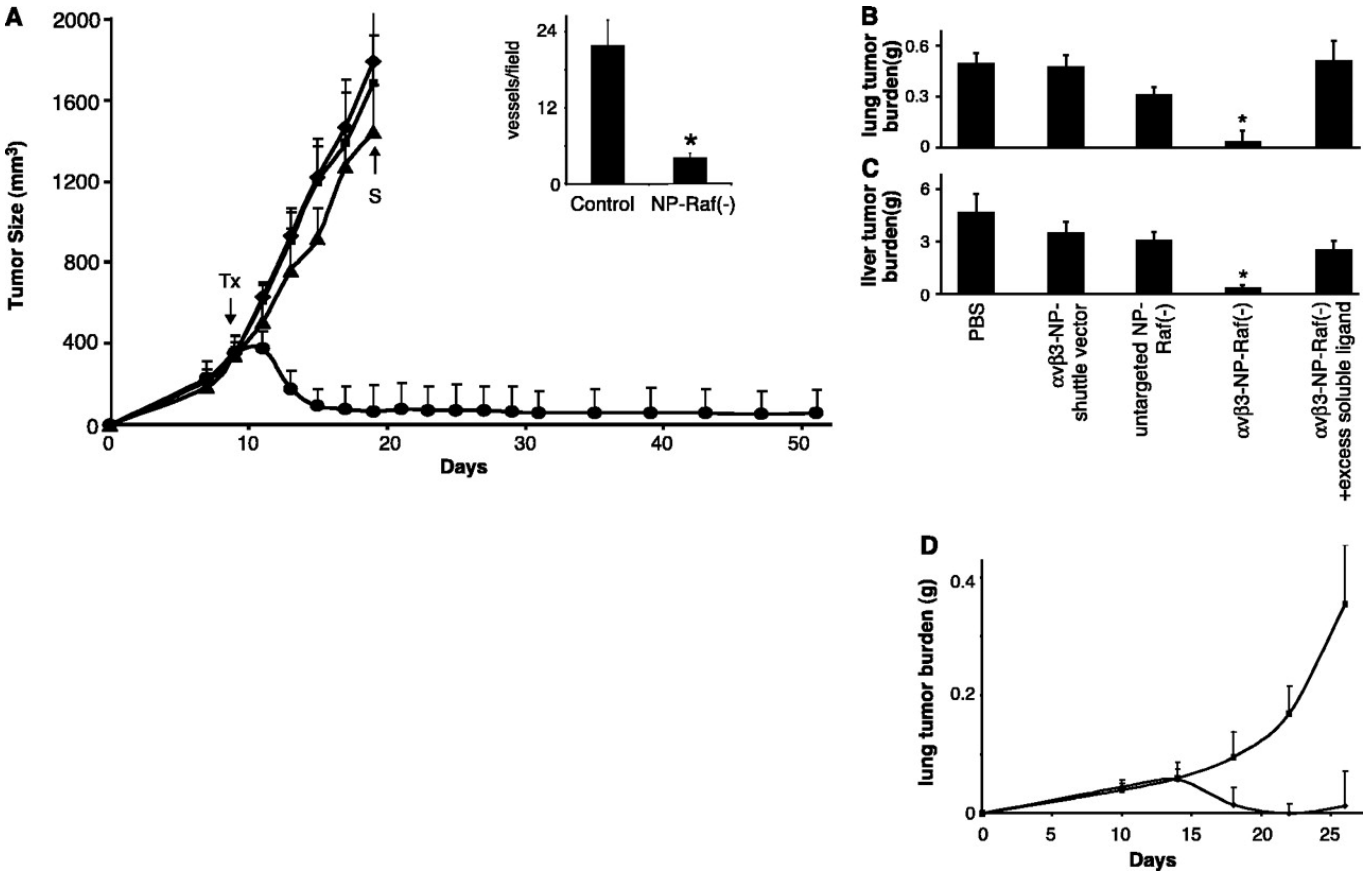
Sipkins DA, et al. Nature Medicine 1998;4:623-626.

Vascular Targeted Gene Therapy



Couzin J. Science 2002;296:2314-2315.

Vascular-targeted Gene Therapy



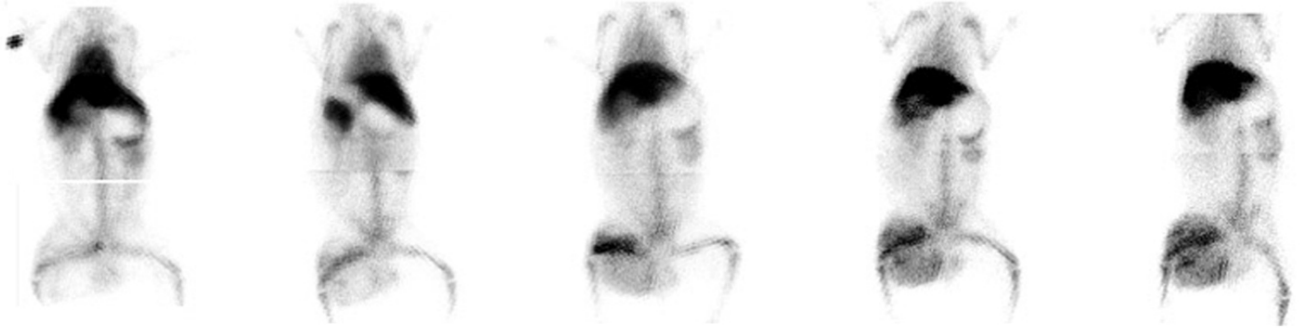
Hood JD, Bednarski M, et al. Science 2002; 296:2404-2407.

Accumulation of LM609-PV in the Vx2 Carcinoma Rabbit

Untargeted PV (^{111}In)

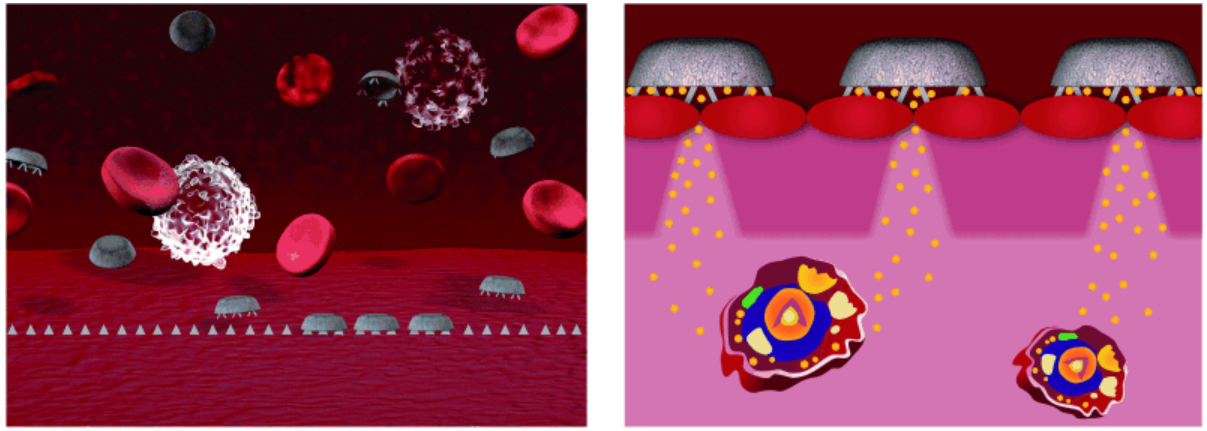
t = 0 | 8 h | 24 h | 48 h | 72 h

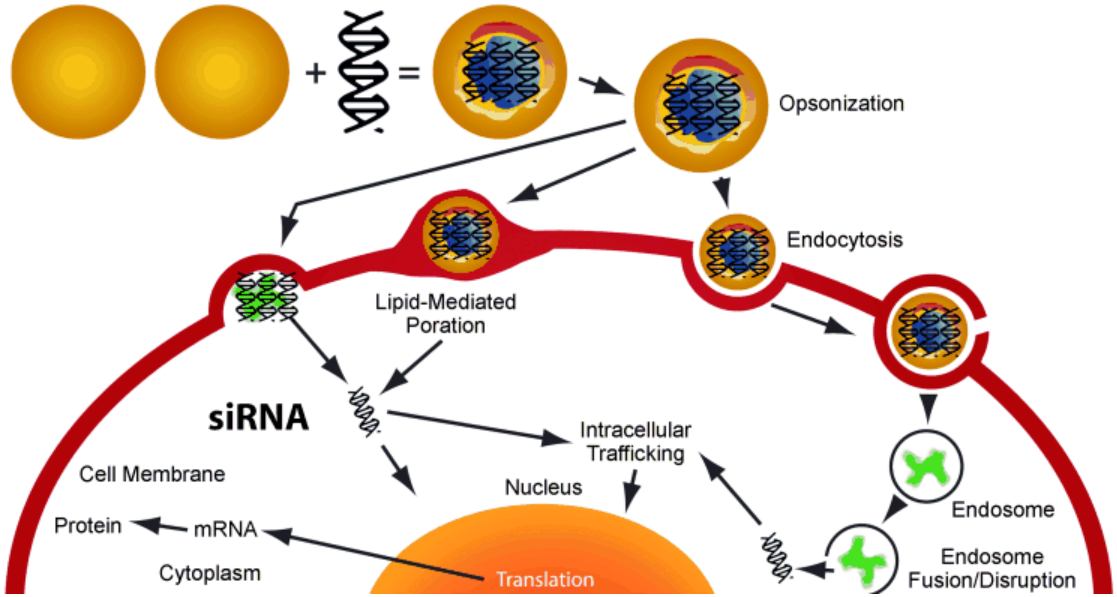
LM609-PV (^{111}In)



t = 0 | 8 h | 24 h | 48 h | 72 h

Multistage Drug Delivery





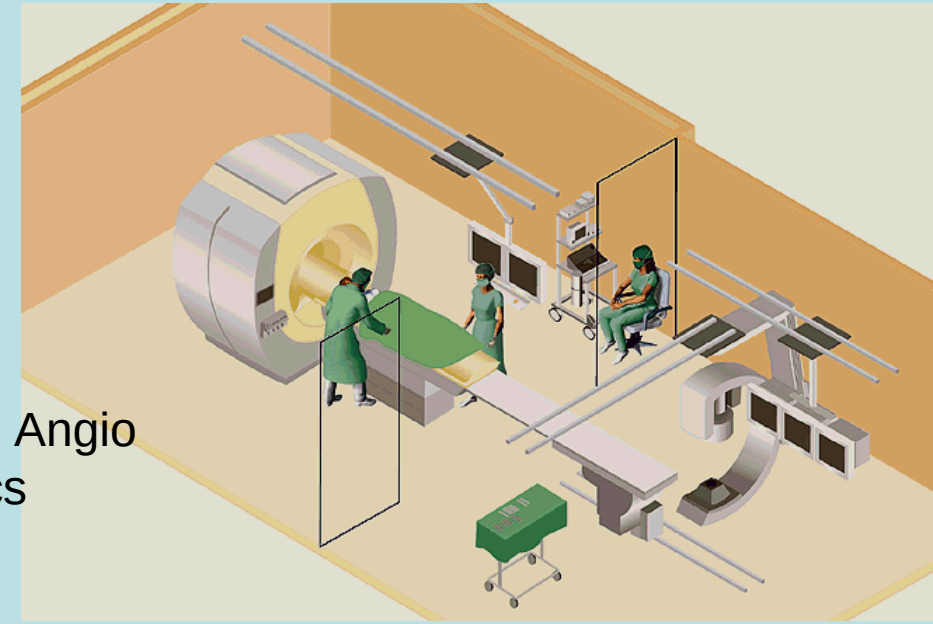
Riehemann K, Scheider SW, et al. Angnew Chem Int Ed 2009;48:872-897.

Bringing the Image to the Patient Cost-effectively

Emerging Technologies Will Add Value

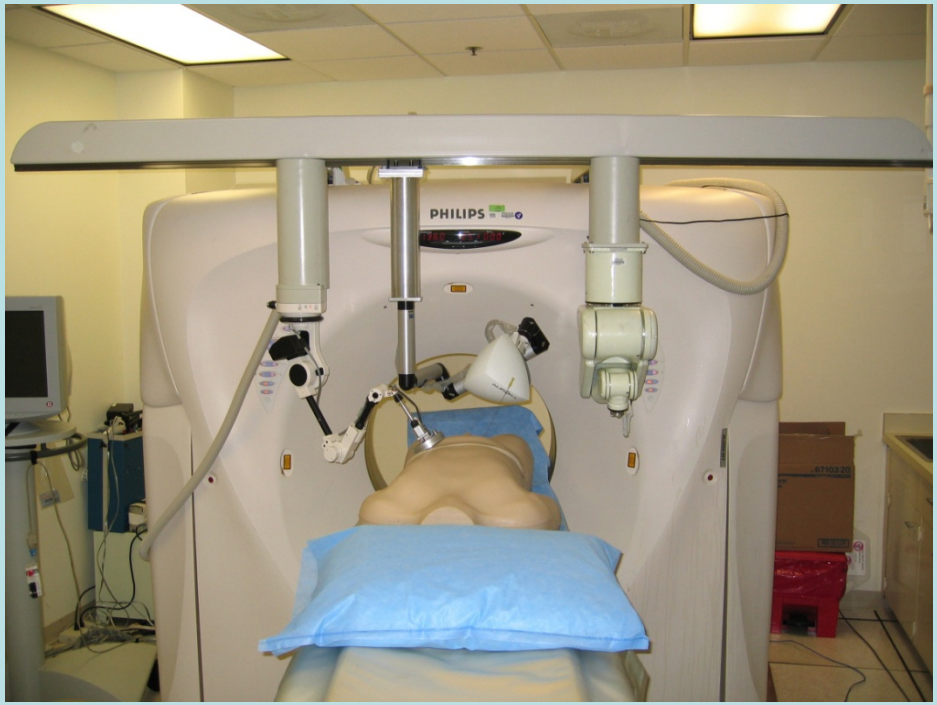
- Automation
- Navigation
- Visualization
- Multimodality
- Fusion
- Drug / Device combo

Multi-modality Infrastructure



Registration “layers” images:

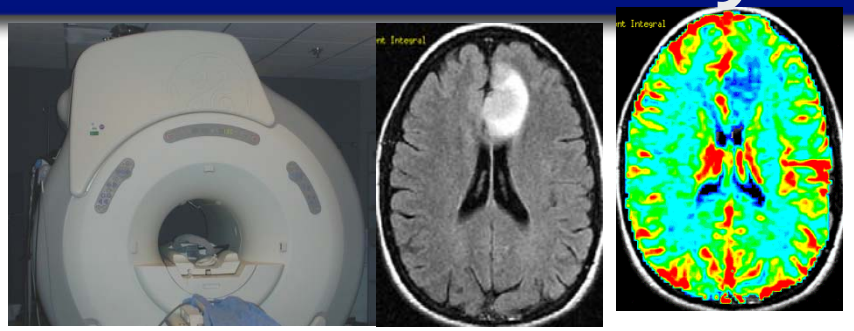
CT + US + Rotational Flat detector Angio
+ γ-imaging + HIFU + Robotics
+ EM Tracking



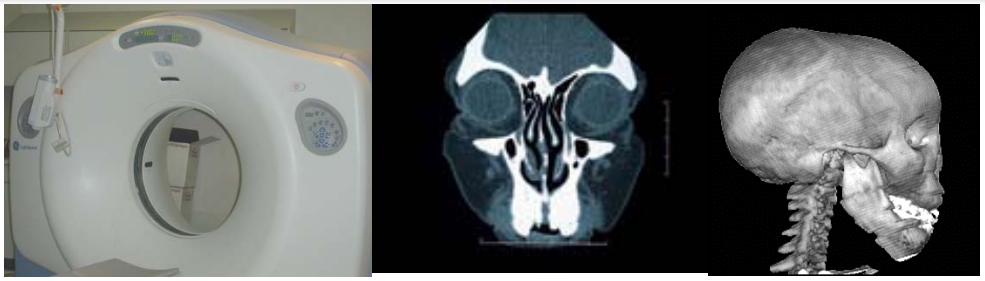
“Remote Controlled Drugs”

- Indentify target tissue
- Change biodistribution to increase concentration of drugs in targeted tissue
- Release or activate drug when needed
- Turn drug effect off when not needed

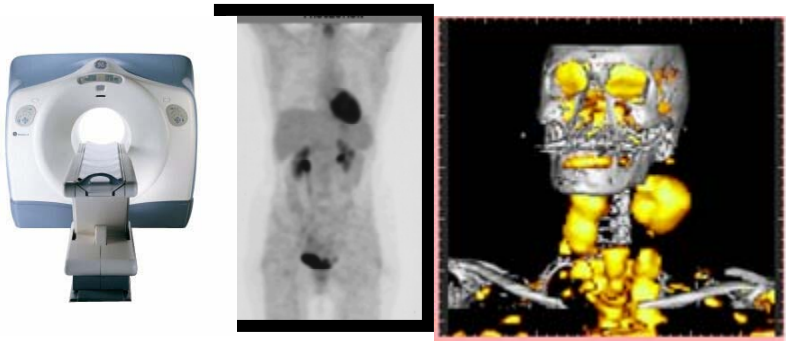
Use Fusion Imaging to identify Target Tissue



Magnetic Resonance Imaging

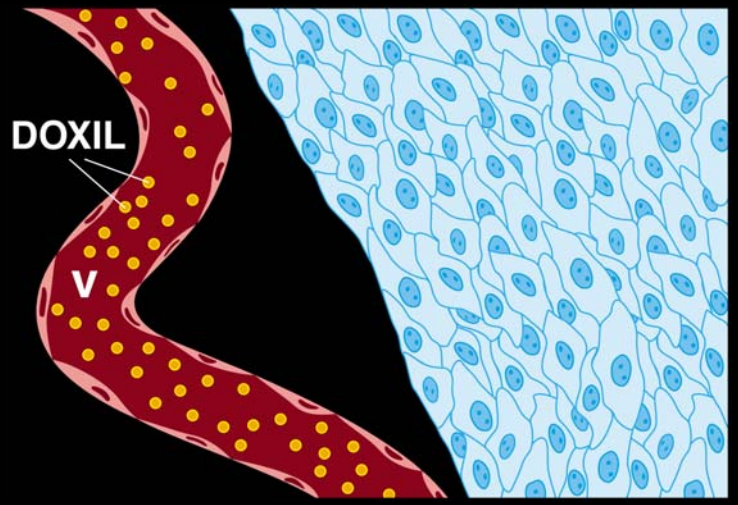


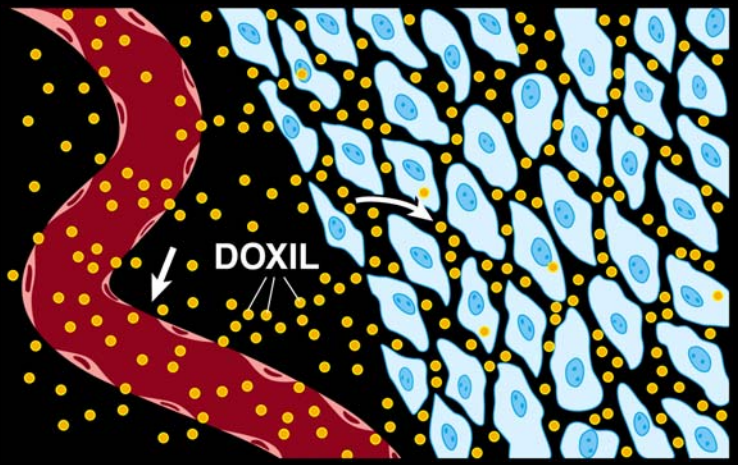
Computed Axial Tomography

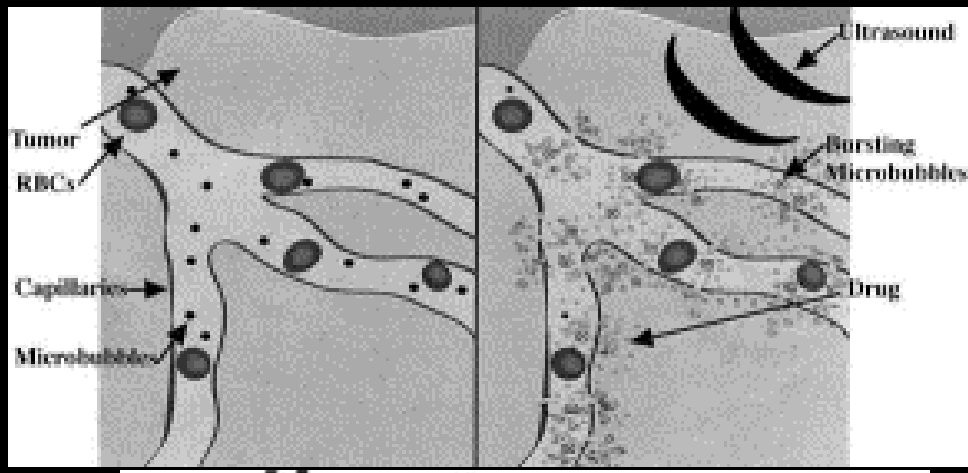


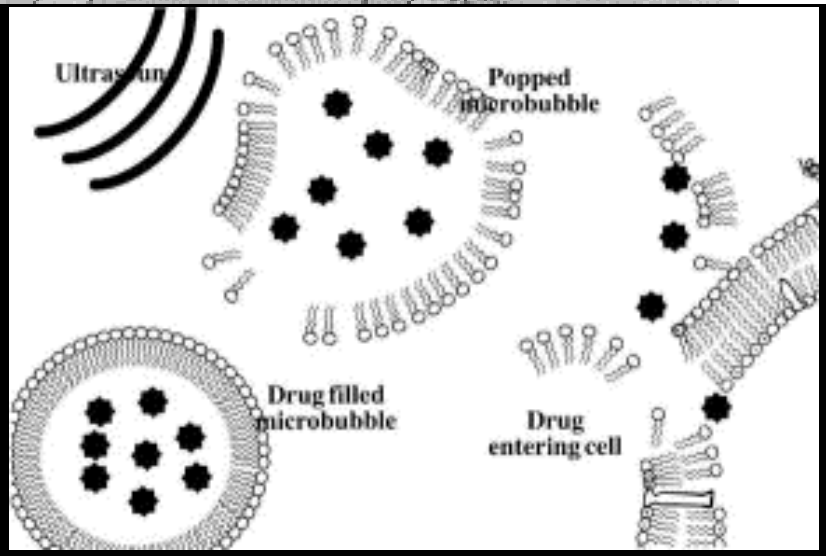
Positron Emission Tomography

Using External Energy such as FUS to change biodistribution of Therapeutic Agents



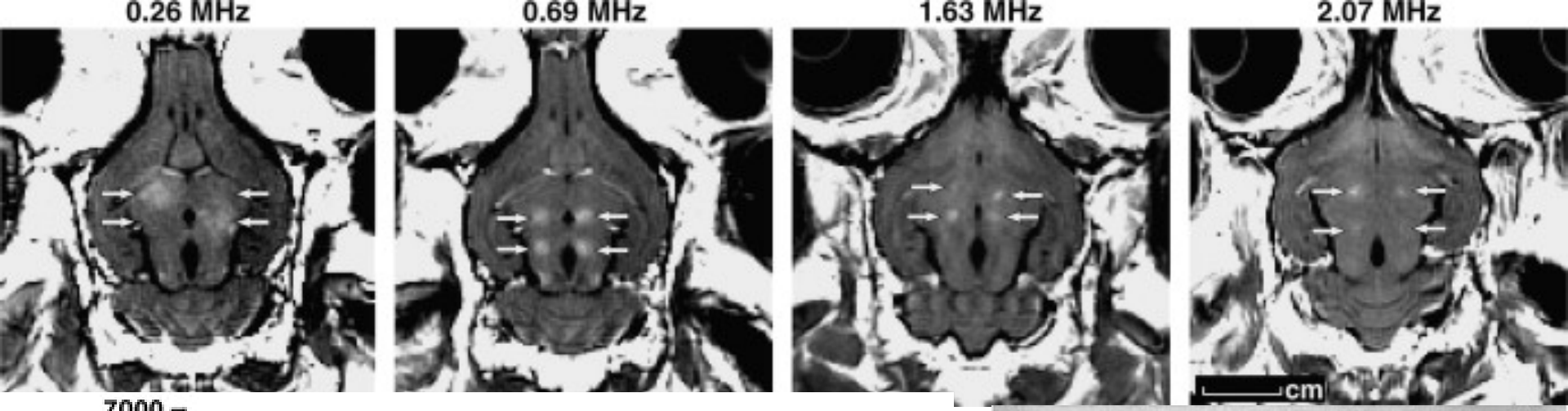


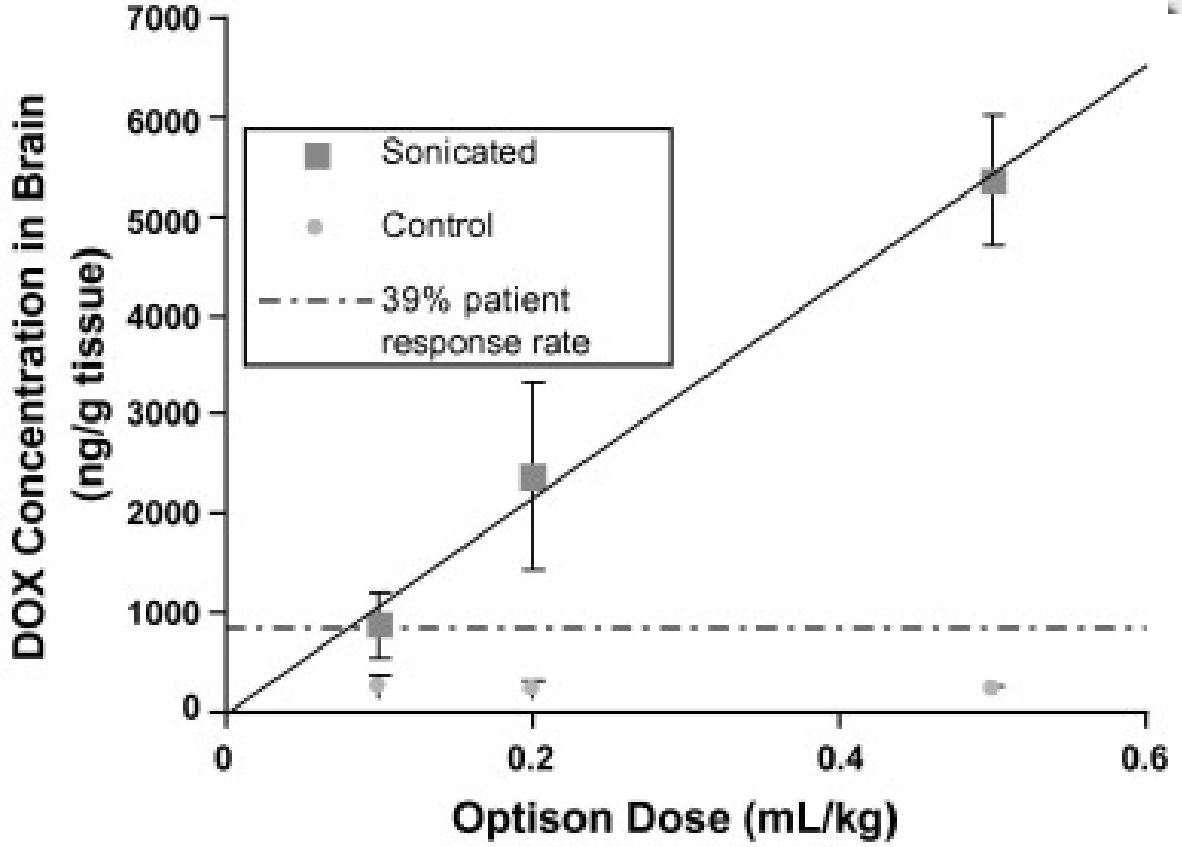


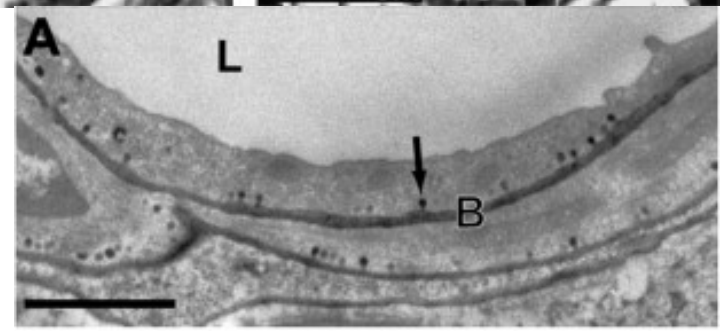


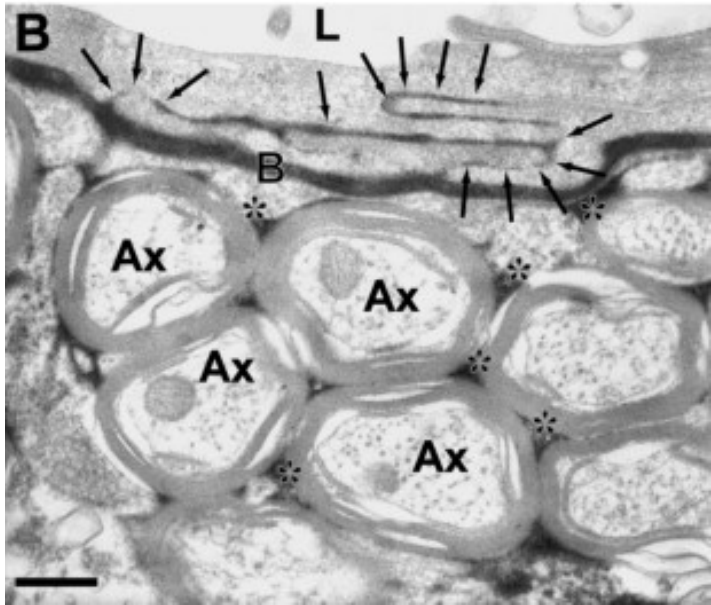
Yuh EL, et al. Radiology 2005;234:431-7.

Unger EC, et al. Progress in Cardiovasc Dis 2001;44:45-54.

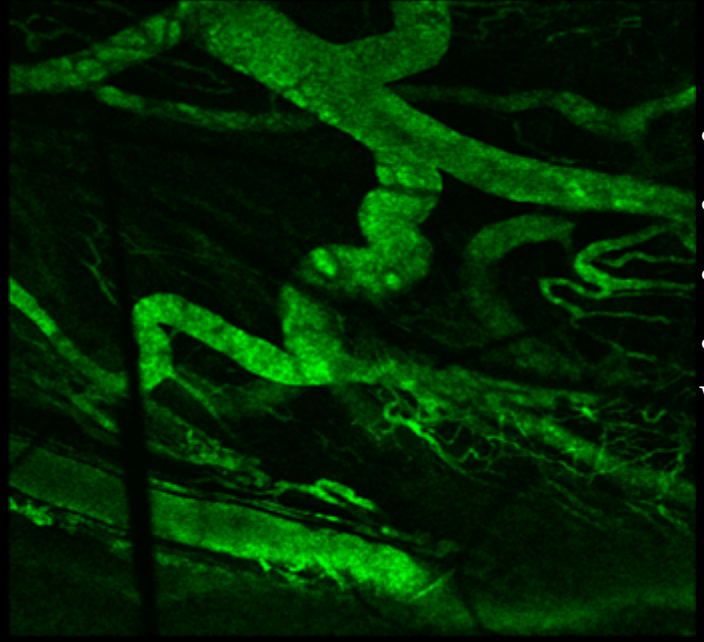




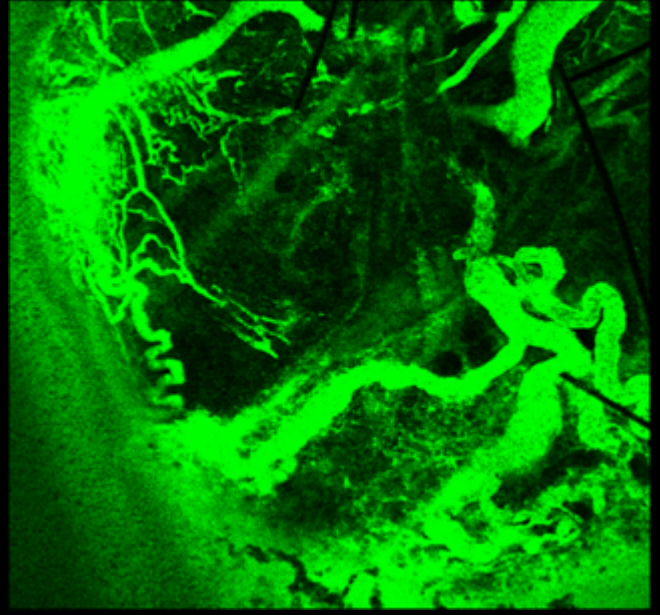




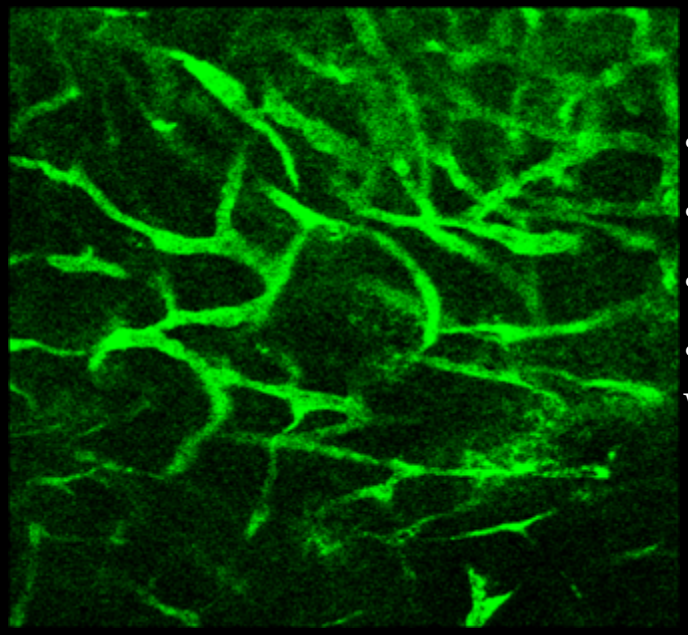
Vykhodtseva N, et al. Ultrasonics 2008; 48:279-296.



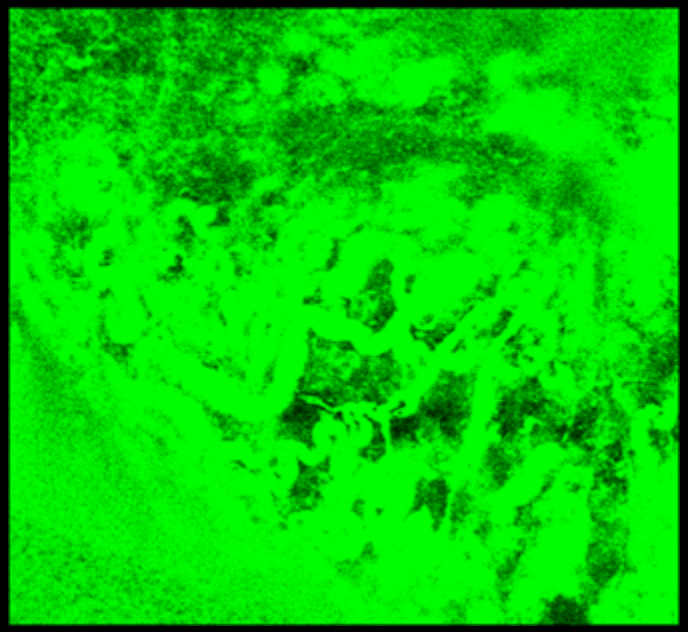
- 30 cycles
- On: 90 msec
- Off: 1910 msec
- Power: 20.5 Watts/cm2



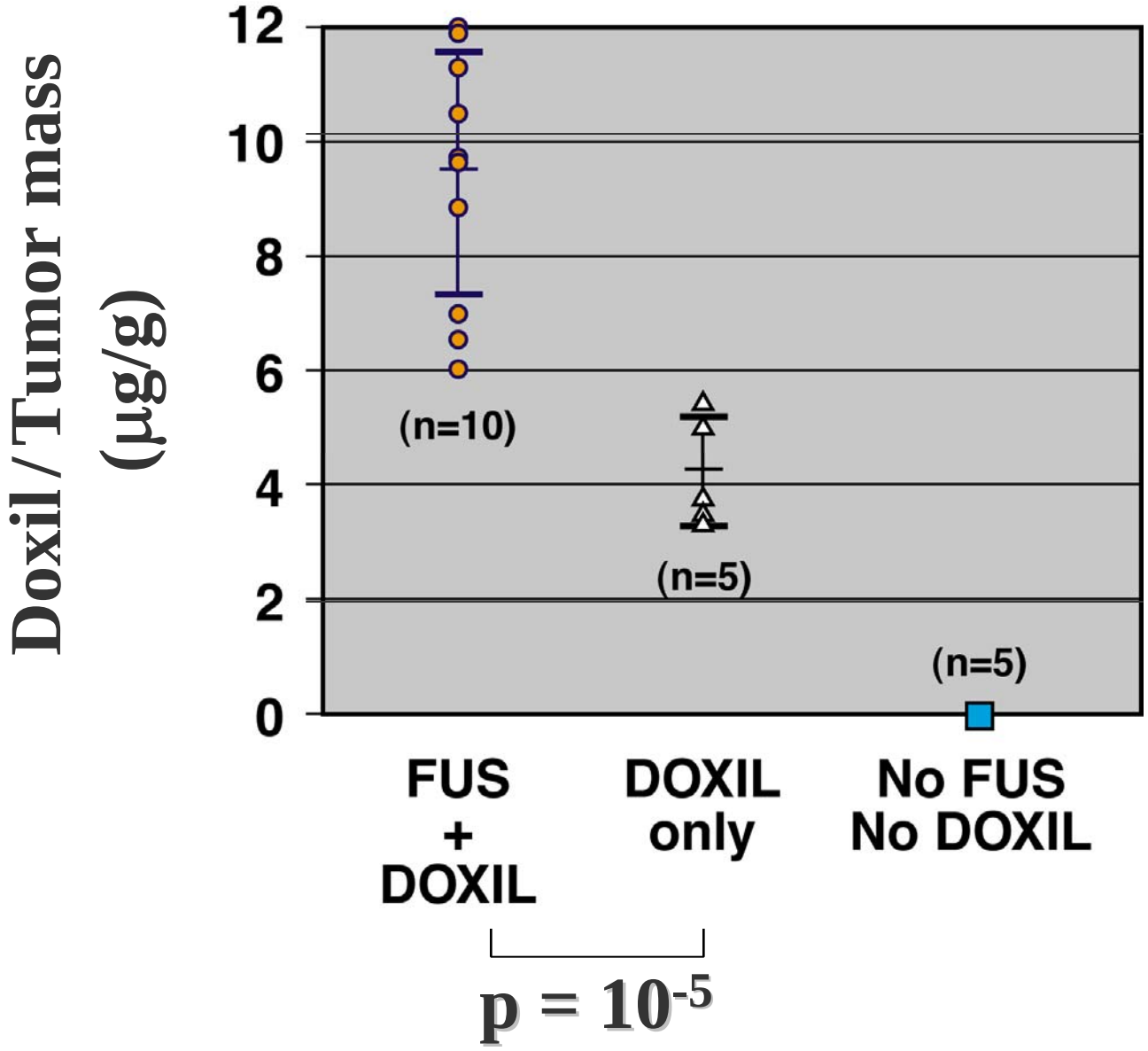
Control **Treated**



- 150 cycles
- On: 90 msec
- Off: 1910 msec
- Power: 20.5 Watts/cm2

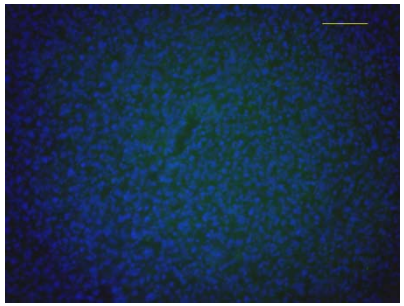


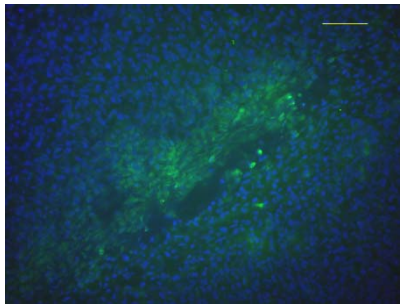
Control **Yuh EL, et al. Radiology 2005;234:431-7.** **Treated**



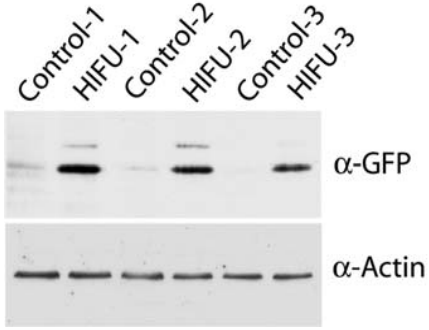
Yuh EL, et al. Radiology 2005;234:431-7.

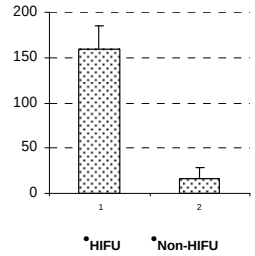
Pulsed-HIFU Facilitated Gene Delivery to Mouse SCC VII Tumors Using I.V. Injected Naked GFP Plasmid





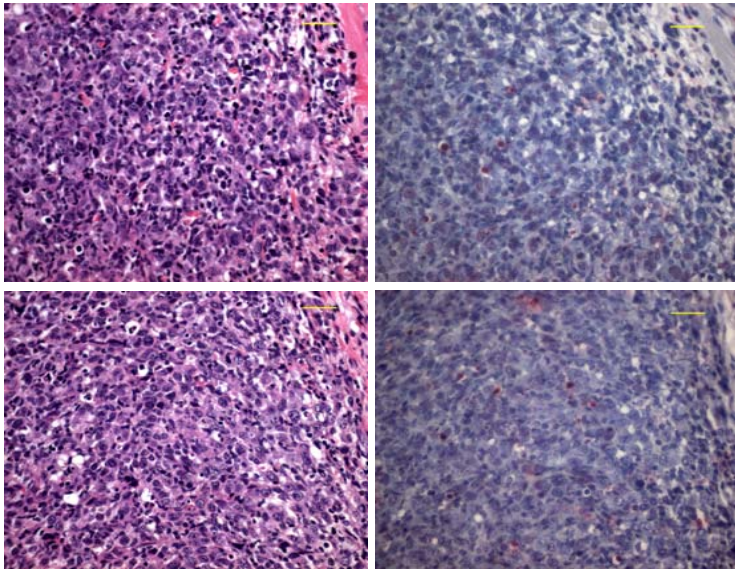
Control **HIFU-Treated**





Western Blot

H&E TUNEL



Treated

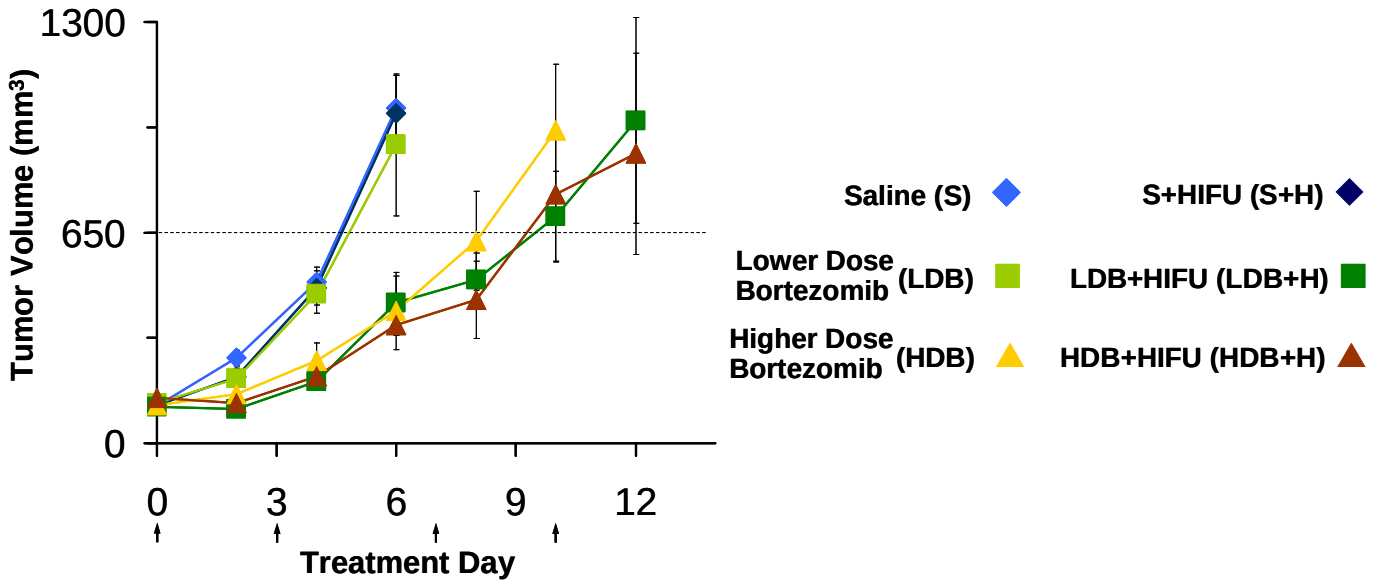
Control

No histologic damage seen in Pulsed-HIFU treated Tissues.

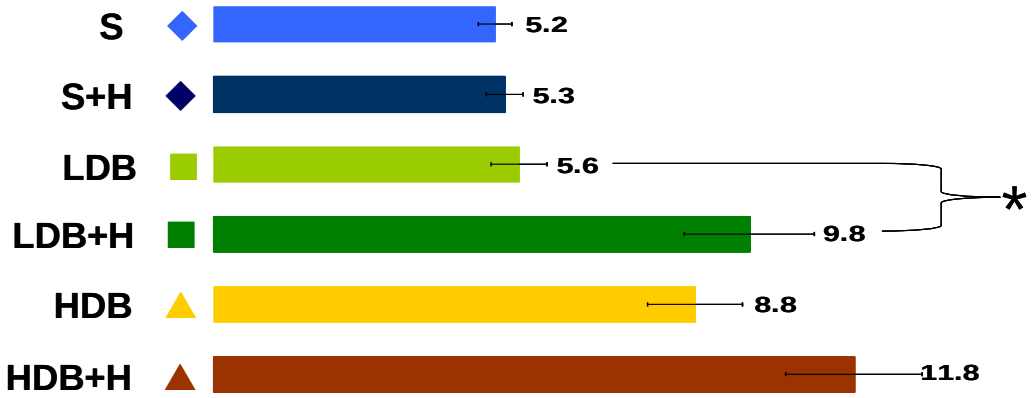
Dittmar K, et al. Radiology 2005;235:541-6.

Pulsed HIFU Facilitated Bortezomib treatment in SCCVII tumors

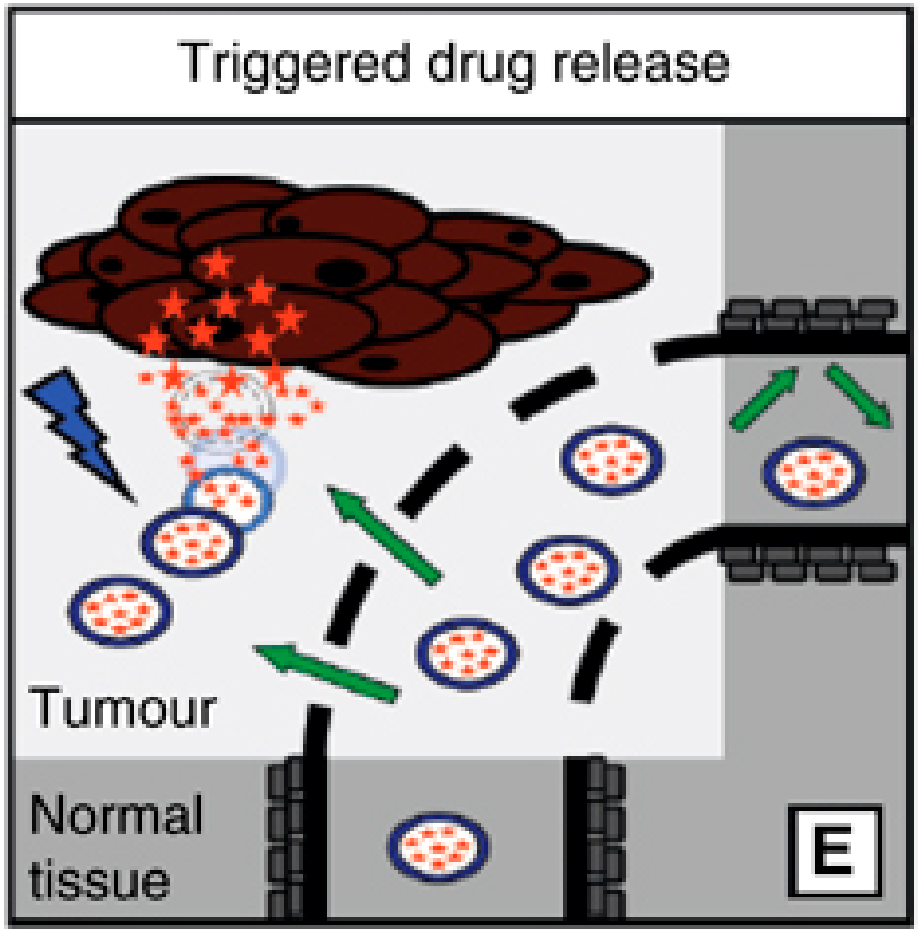
•A.



•B.



External Energy triggered drug release

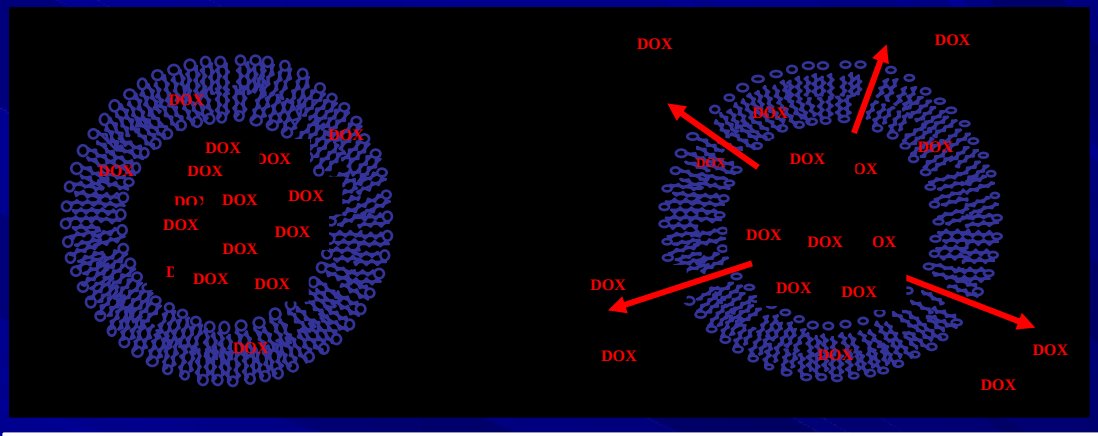


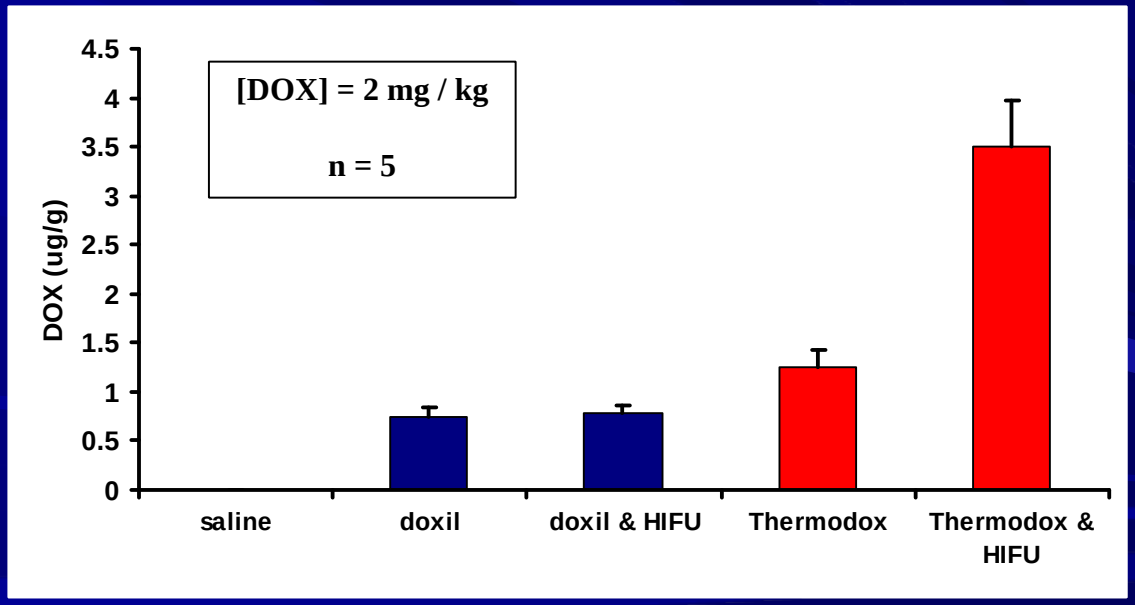
Microbubble Drug Formulations

Heat Sensitive Liposomes

Lammers T, et al. British Journal of Cancer 2008;99:392-397.

Low Temperature Heat Sensitive liposomes (Thermodox™)

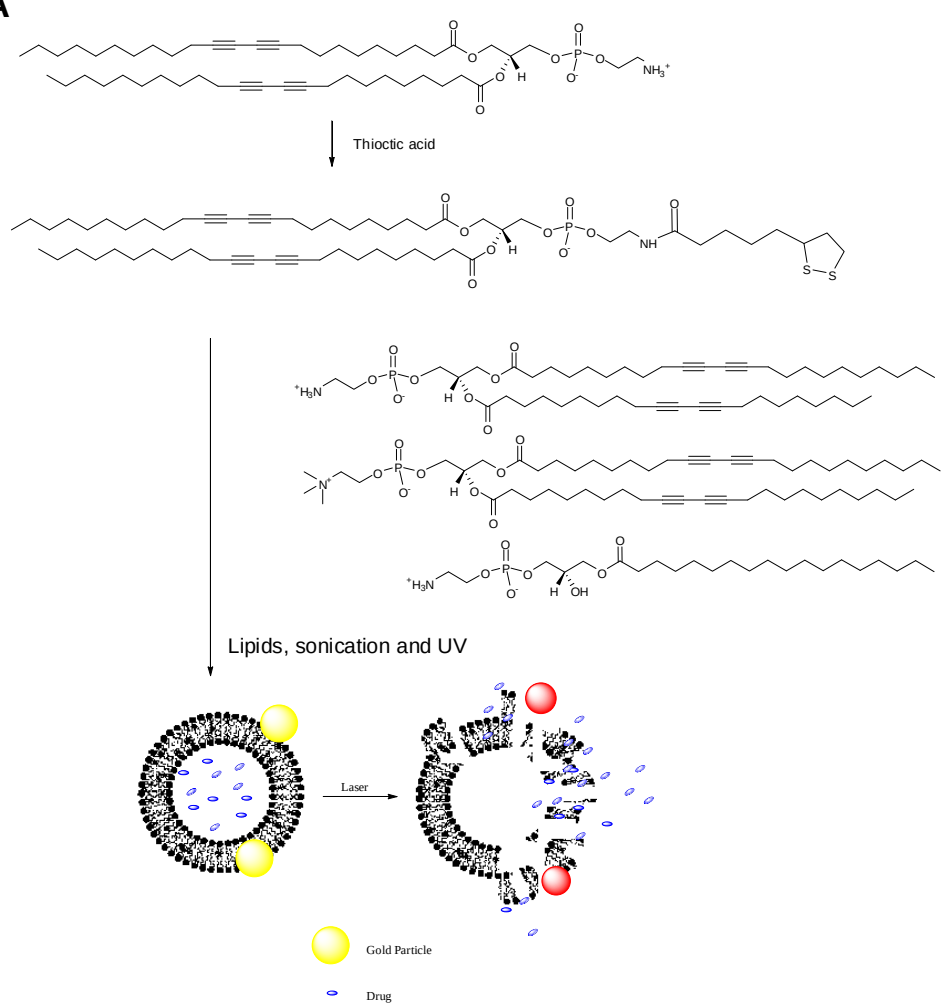




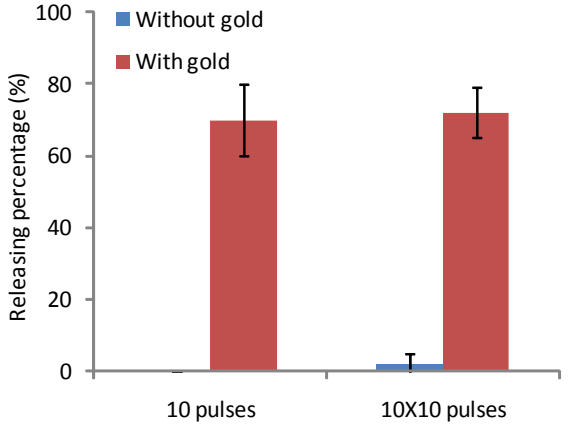
Dromi et al. 2007 Clin. Cancer Res.

Gold Labeled Partially Polymerized Liposomes

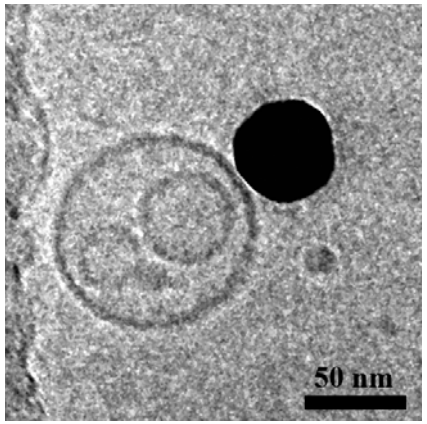
A



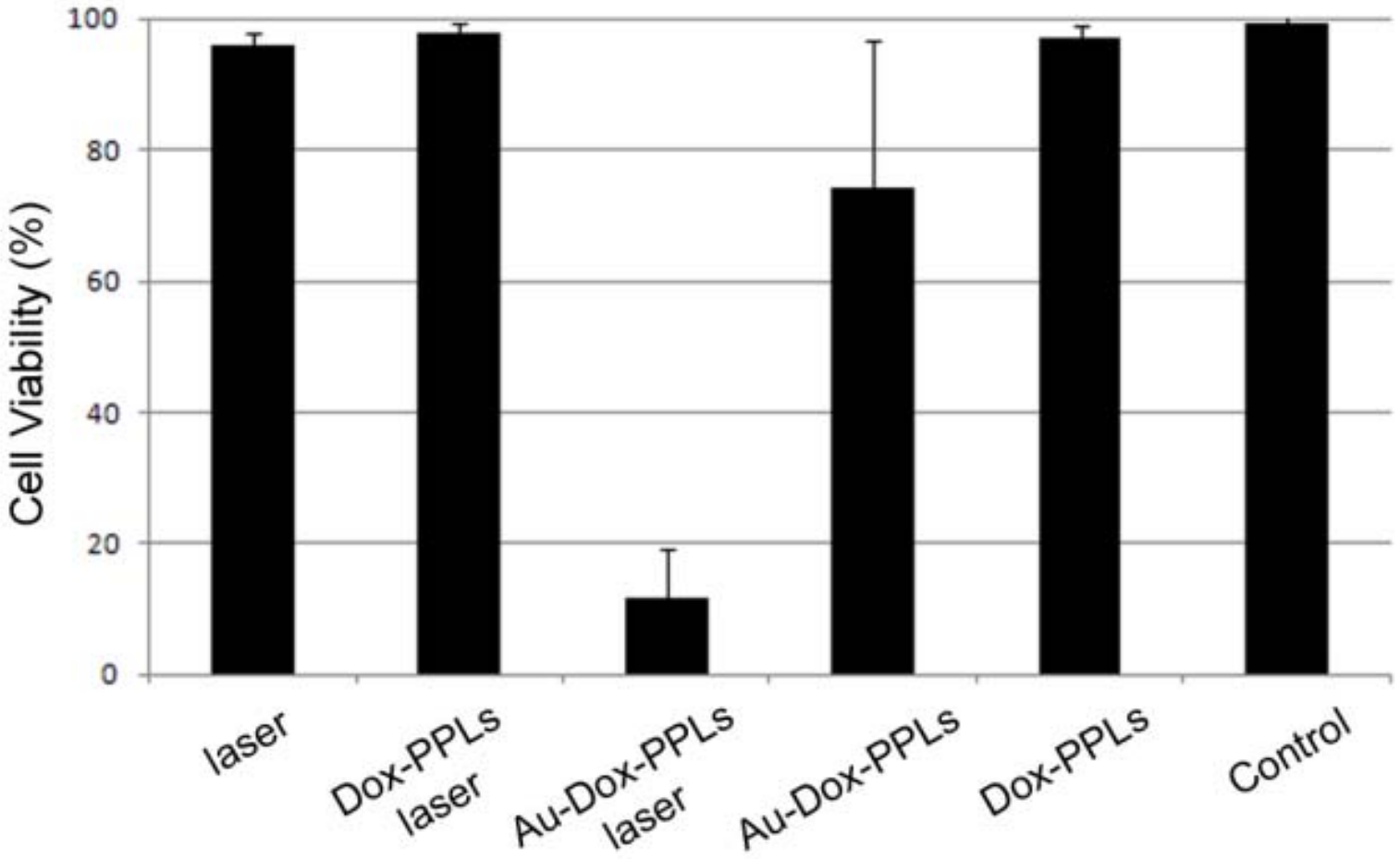
B



C



Laser triggered Au-Dox-PPLs Influence on Pharmacodynamics



Points to consider for Clinical Translation of Cancer Nanomedicine

- Pharmacokinetcs and Pharmacodynamics (Special ADME considerations and difficulty in tracking multiple components in vivo over time)
- Biocompatible vs. non-biocompatible components
- Passive vs. Active Targeting
- Multi-stage nanoparticles vs. different strategies for different stages (leveraging other delivery strategies to make nanoparticle design simpler?)
- Activatable vs. Always On
- Sensitive to local environment vs. external stimulation vs. combination

Targeted Drug Delivery