Cancer Nanomedicine

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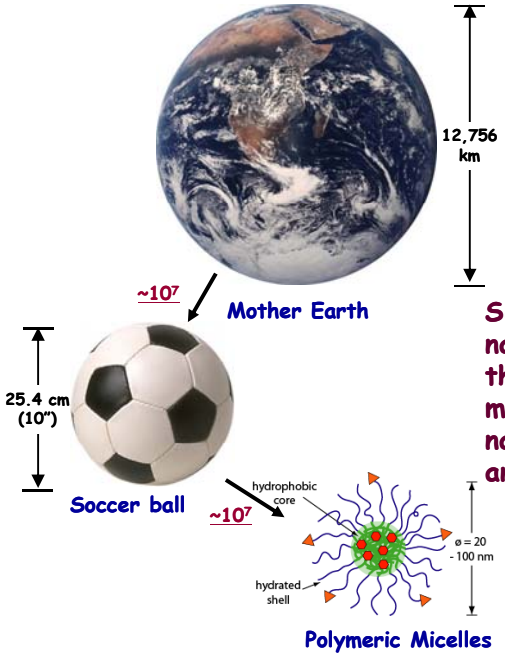
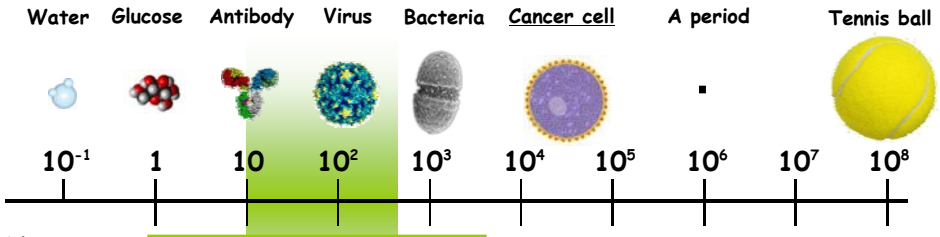
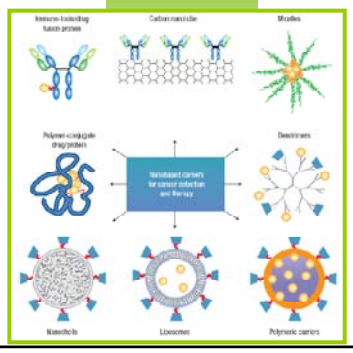
Nanomedicine in Perspective



Significant breakthrough in nanotechnology makes it feasible the development of multifunctional cancer nanomedicine for early detection and treatment of cancer

Nano Delivery Systems

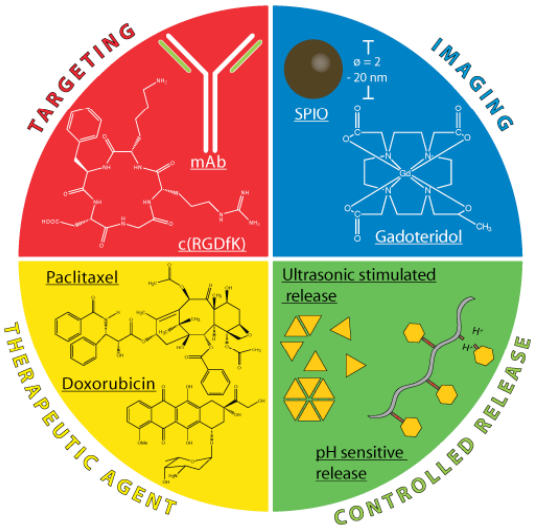




Nanomed Systems:
Polymer-drug conjugates
Polymer micelles
Liposomes
Dendrimers
Nanotubes
Quantum dots
Nanoshells
...

Peer et al, Nat. Nanotech. 2007
Ferrari, Nat. Rev. Cancer, 2005

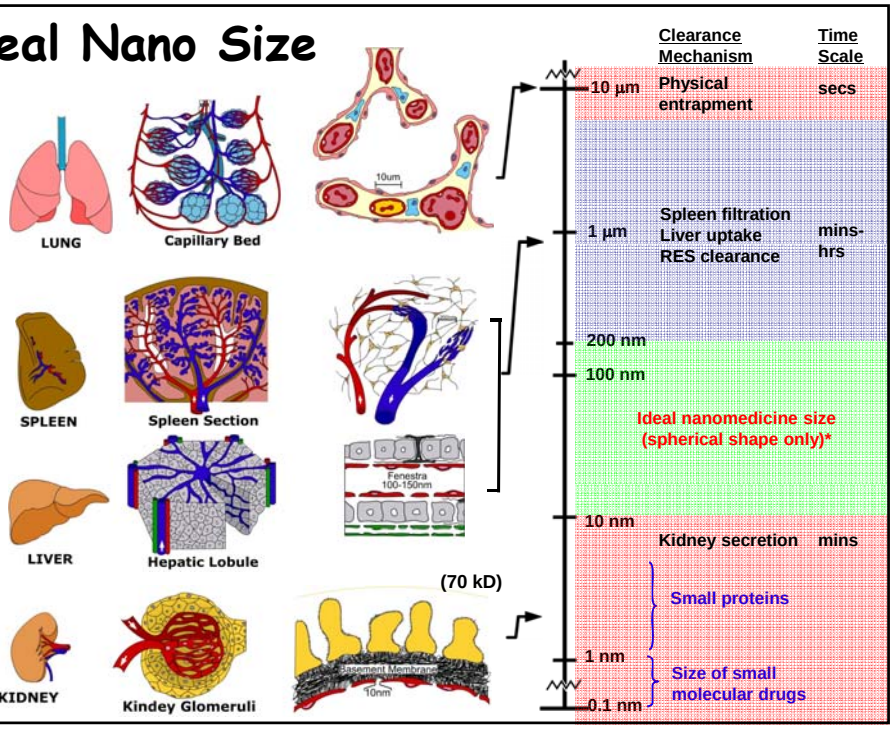
Multi-Functional Nanomedicine for Cancer



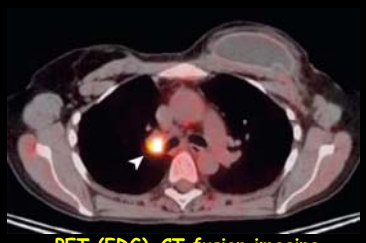
- Tumor heterogeneity and adaptive resistance are major challenges in cancer chemotherapy
- Nanomedicine aims for targeted delivery and controlled release of multiple anticancer agents to maximize efficacy
- Imaging functions provide molecular diagnosis and monitoring of efficacy
- Personalized "theranostic" nanomedicine

Gao & Sumer Nanomedicine, 2008

Ideal Nano Size

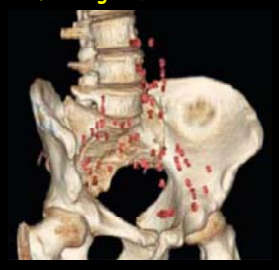


Molecular Imaging



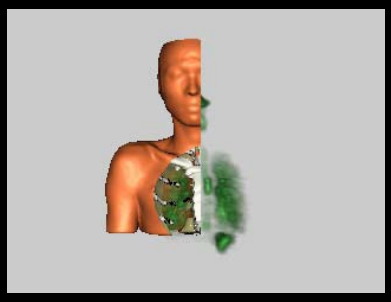
PET (FDG)-CT fusion imaging of a lung tumor in a cancer patient

- Early detection of disease
- Post-therapy assessment
- Pharmacokinetic imaging



MRI (MION)-CT fusion imaging of cancer metastases (red dots) in pelvic lymph nodes from prostate cancer

Jaffer & Weissleder, *JAMA*, 2005



3D Hybrid rendering of PET-measured *in vivo* radio-aerosol deposition (green) with half of the body from CT scan.

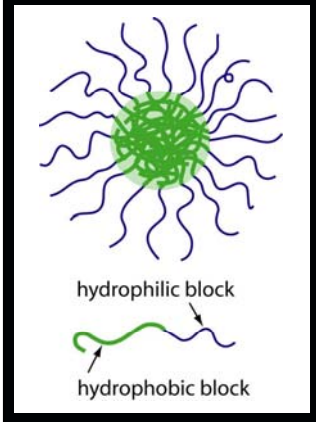
Lee, CWRU

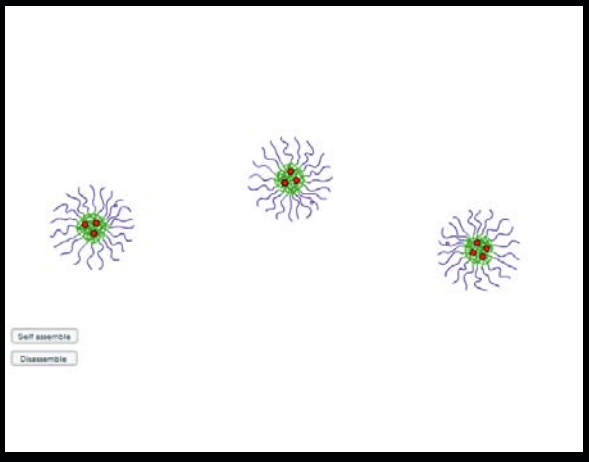
Nanomedicine Platforms

Nano Systems	Polymer-drug conjugates 	Dendrimers 	Polymer micelles 	Liposomes 
Size	< 10 nm	2-10 nm	10 - 100 nm	100 - 200 nm
Structural characteristics	Macromolecular structure	Macromolecular tree-like structure	Spherical, supramolecular core-shell structure	Spherical, bilayer vesicle structure
Carrier Composition	Water-soluble polymer	Hyperbranched polymer chains	Amphiphillic di- and tri-block copolymers	Phospholipid, cholesterol membrane lipids
Drug incorporation strategy	Covalent conjugation requiring functional groups on drug and polymer	Covalent conjugation requiring functional groups on drug and polymer	Non-covalent encapsulation/ compatible with hydrophobic drugs	Non-covalent encapsulation/ compatible with hydrophillic drugs
Clinical status	Clinical	Preclinical	Phase I/II clinical trials	Clinical

Exp. Biol. Med. 2008.

Polymeric Micelles

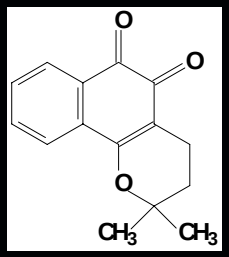




- Core-shell-type assemblies from amphiphilic polymers
- Hydrophobic core provides a natural carrier environment for hydrophobic drugs

β-Lapachone

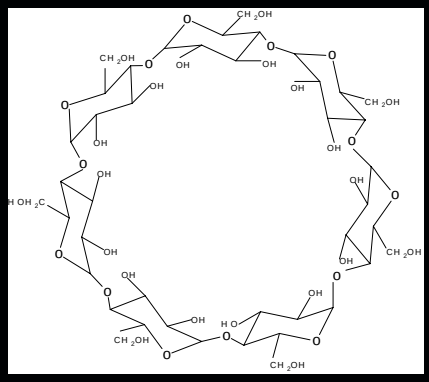
- Isolated from the bark of Lapacho tree in South America
- Mechanism dependent on NQO1 enzyme-catalyzed depletion of NAD(P)H
- Elevated expression of NQO1 enzyme in many cancer cells, including breast, lung and prostate.
- Kiss of death: irreversible cell death in ~4 hrs; no drug resistance has been observed
- Very low solubility: 0.04 mg/cc



David Boothman

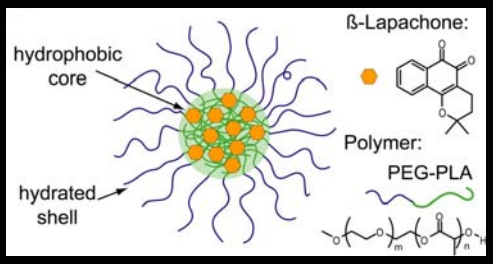
ArQ501: β-lap/HPβ-CD complex

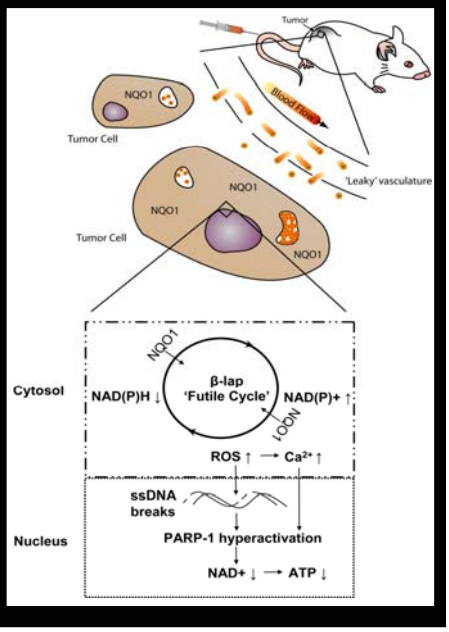
- Phase II clinical trials
- Hydroxyl propyl-β-CD inclusion complex
- Solubility increases from 0.04 to 16 mg/mL
- Intraveneous injection at 400 mg/m^2 dose
- Hemolysis is a major side effect in patients



J. Pharm. Sci. 2004

β-Lapachone Nanomedicine

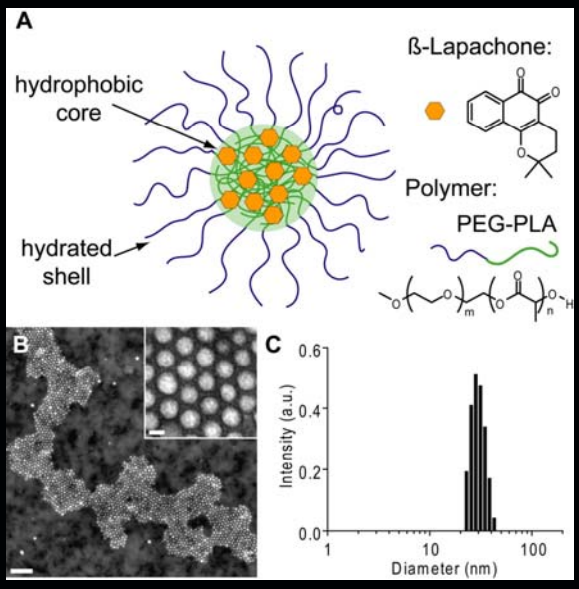




Hypothesis

Combination of a novel therapeutic agent and effective drug delivery system will provide an efficacious nanomedicine for lung cancer therapy

β-Lapachone Micelles



Blanco, et al, JCR, 2005

Acute Toxicity

HPβ-Cyclodextrin

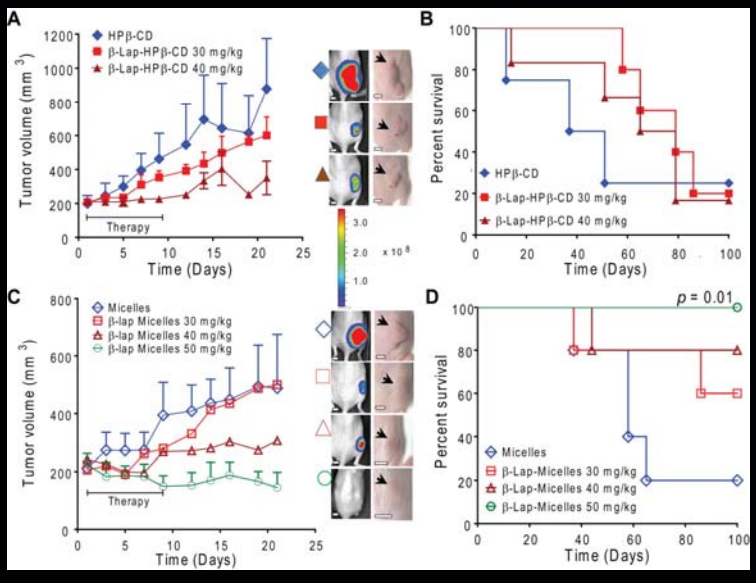
PEG-PLA micelles

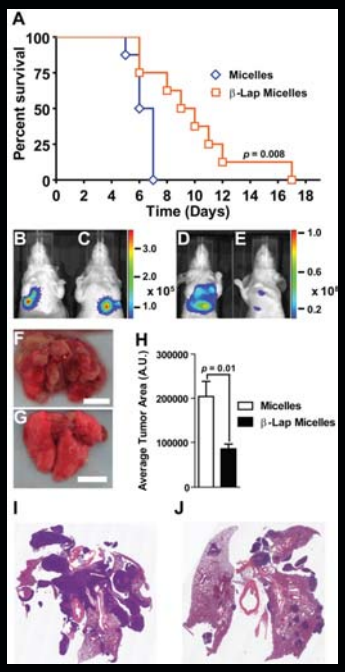
30 mg/kg dose

Blanco, Bey

Antitumor Efficacy

Human A549 lung tumor xenograft in nude mice (subQ)



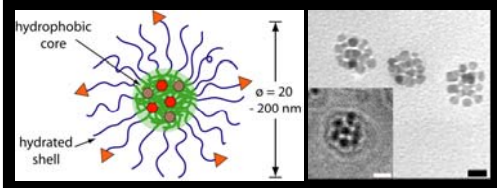


Antitumor Efficacy

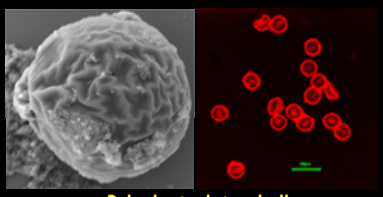
- Orthotopic lewis lung carcinoma in athymice nude mice
- Micelles were injected i.v. via tail vein e.o.d. 5 times at 40 mg/kg dose
- Efficacious response from survival, BLI, histology analyses

Blanco, Bey, et al, JNCI, submitted

Nanomedicine Platforms at UTSW

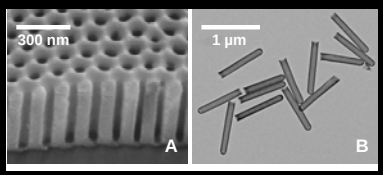


Multi-functional polymeric micelles

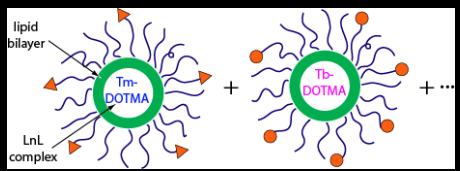


Polyelectrolyte shells

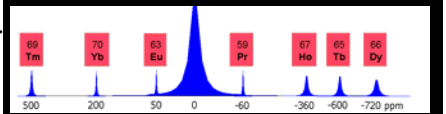
Cancer-specific quantum dots



Nanotubular capsules



"Multi-colored" MRI probes



Lanthanide shifting agents