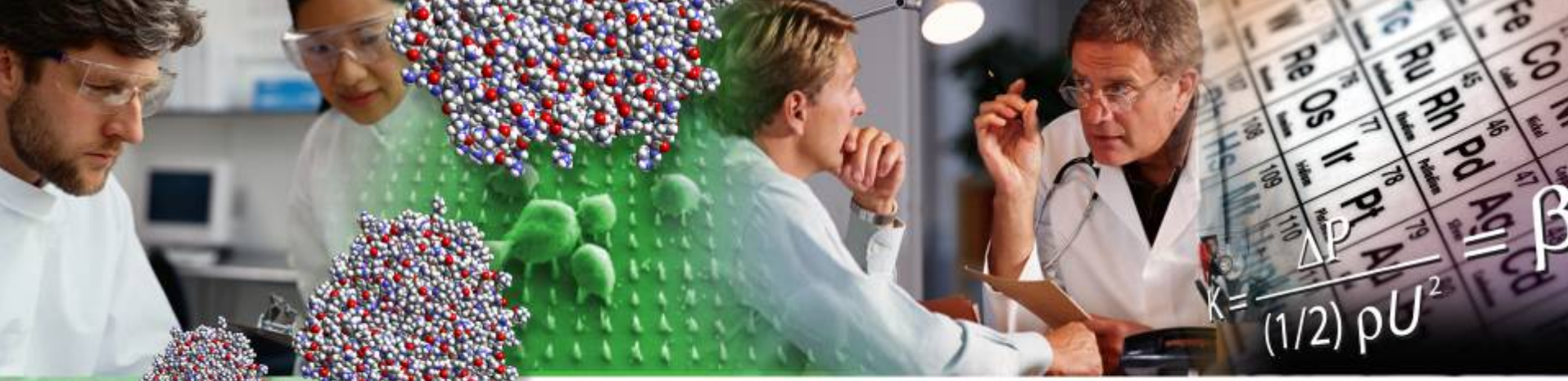


NCI Alliance for Nanotechnology in Cancer

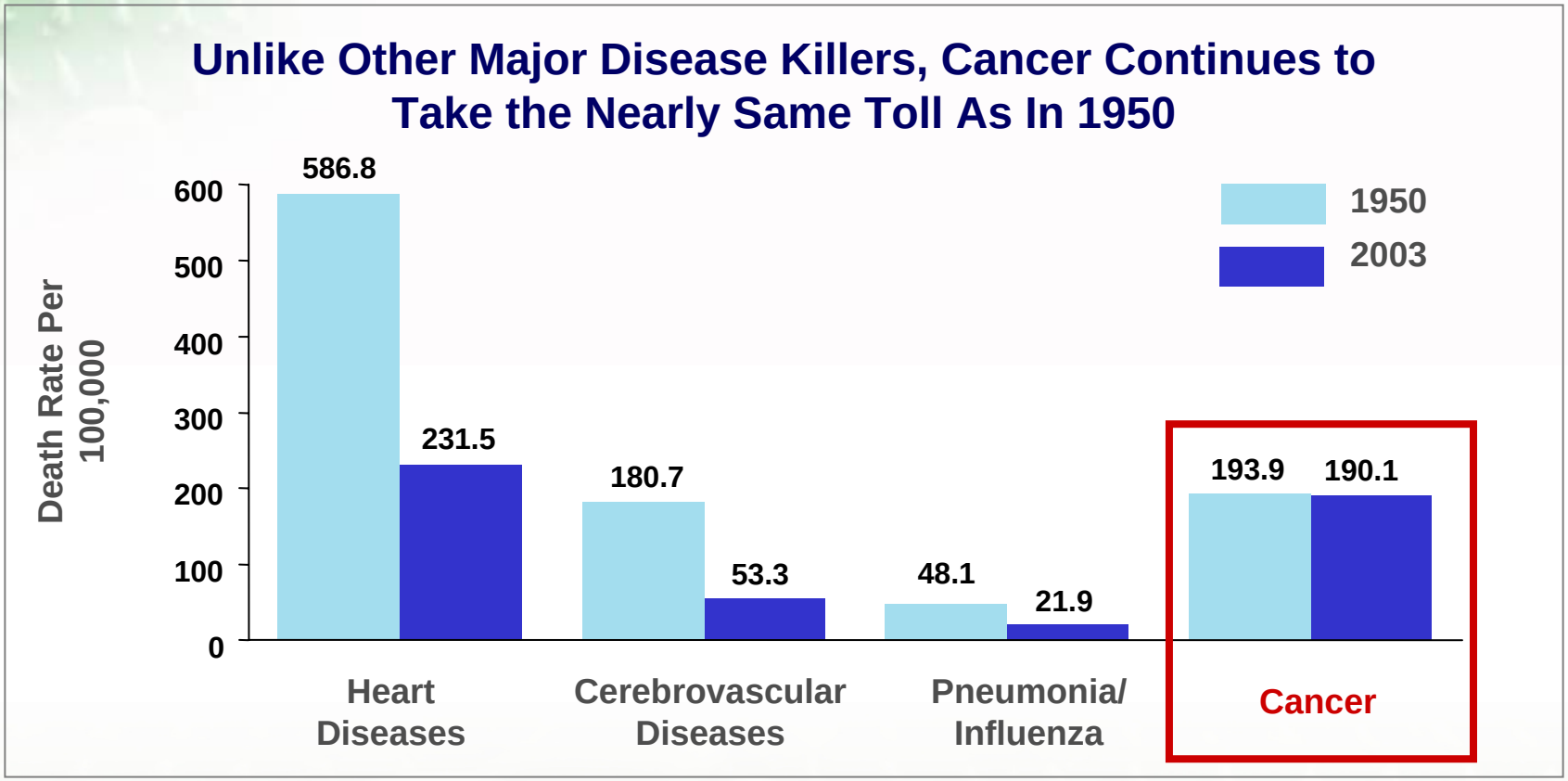
The Workings of NCI Nanotechnology Alliance for Cancer – an Opportunity for a New Class of Diagnostic and Therapeutic Solutions Based on Nanotechnology

NSF Nanoscale Centers Grantees Conference
Washington, DC
December 5, 2007

Piotr Grodzinski, Ph.D.
Director, NCI Nanotechnology Alliance
National Cancer Institute

We Must Accelerate Progress Against Cancer

NCI Alliance for Nanotechnology in Cancer



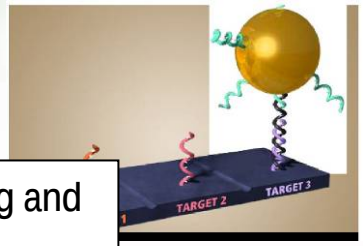
Source for 2005 deaths and diagnoses: American Cancer Society (ACS) 2005 Cancer Facts & Figures; Atlanta, Georgia
Source for 2003 age-adjusted death rate: National Center for Health Statistics, U.S. Department of Health and Human Services, NCHS Public-use file for 2003 deaths.

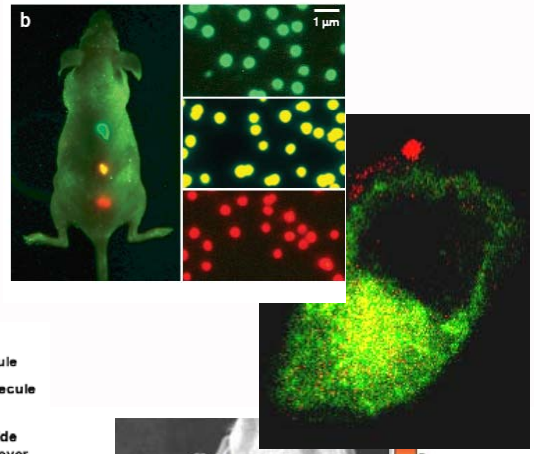
Nanotechnology is an Enabler of New Solutions for Cancer

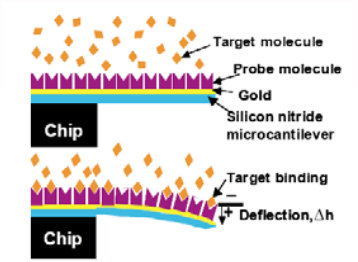
NCI Alliance for Nanotechnology in Cancer

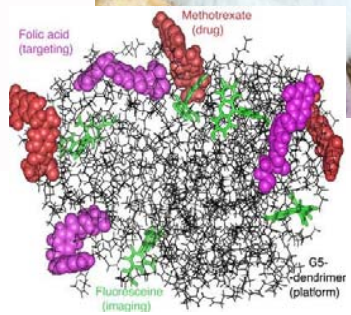
Focus Areas:

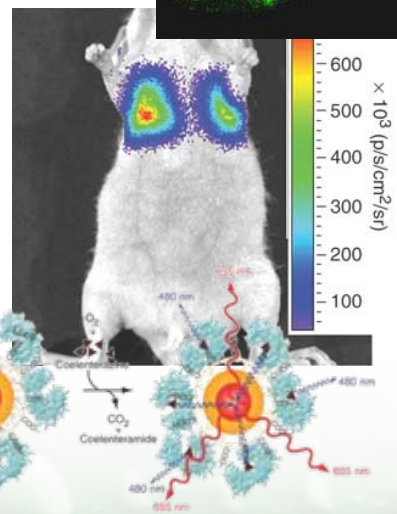
- Molecular imaging and early detection
- In vivo imaging
- Reporters of efficacy
- Multifunctional therapeutics
- Prevention and control
- Research enablers

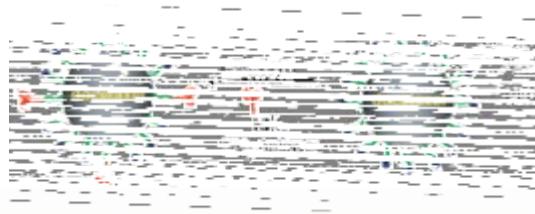












Early detection

Imaging

Therapy

NCI Nanotechnology Alliance
The Opportunity

NCI Alliance for Nanotechnology in Cancer

- promote the development of state-of-the-art nanotechnologies for cancer applications
- accelerate the translation of the discoveries into clinically relevant diagnostics and therapeutics

Highly talented multi-disciplinary research teams

↓

Sciences, medicine, and engineering
Competition and collaboration
Synergy and difference

↓

Can we build a bigger whole?

NCI Nanotechnology Alliance - Strategies

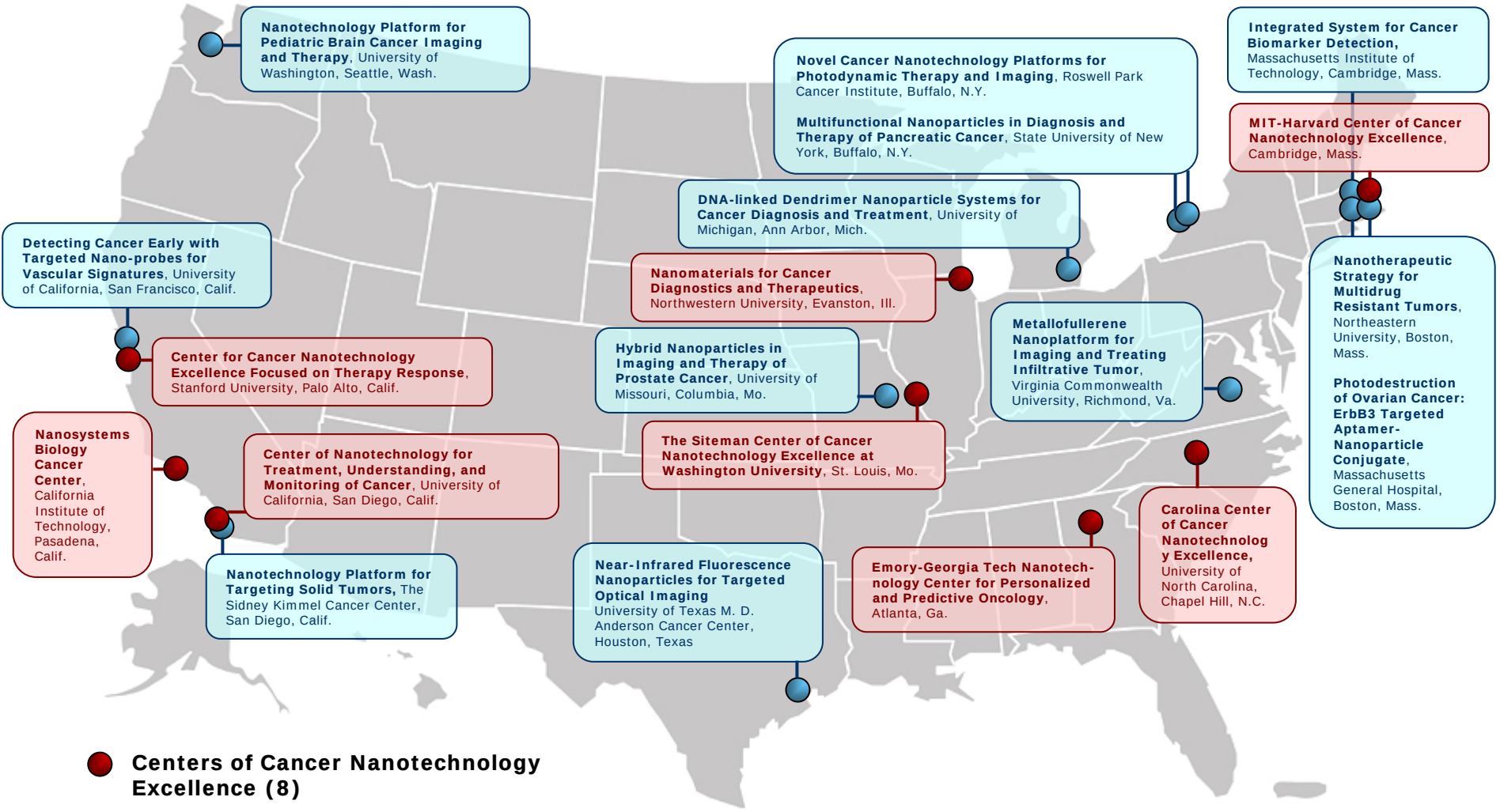
NCI Alliance for Nanotechnology in Cancer

Major Programs of the Alliance:

1. Centers of Cancer Nanotechnology Excellence
2. Multidisciplinary Research Teams
   - Training
   - Interagency Collaborations
3. Nanotechnology Platforms for Cancer Research
4. Nanotechnology Characterization Laboratory

NCI Nanotechnology Alliance - Awards

NCI Alliance for Nanotechnology

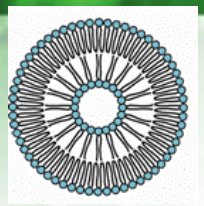


Centers of Cancer Nanotechnology Excellence (8)

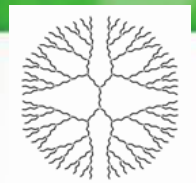
Cancer Nanotechnology Platform Partnerships (12)

Clinical Applications Using Nanoparticles

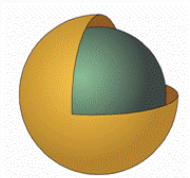
NCI Alliance for Nanotechnology in Cancer



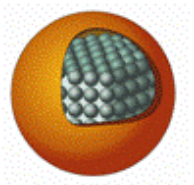
Liposome



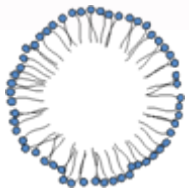
Dendrimer



Gold nanoshell

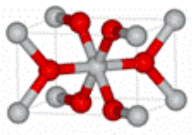


Quantum Dot

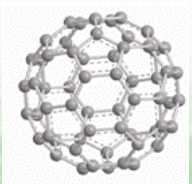


Nanoemulsion

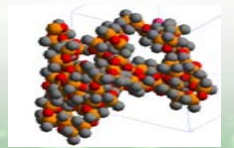
Colloidal gold



TiO_2



Fullerene



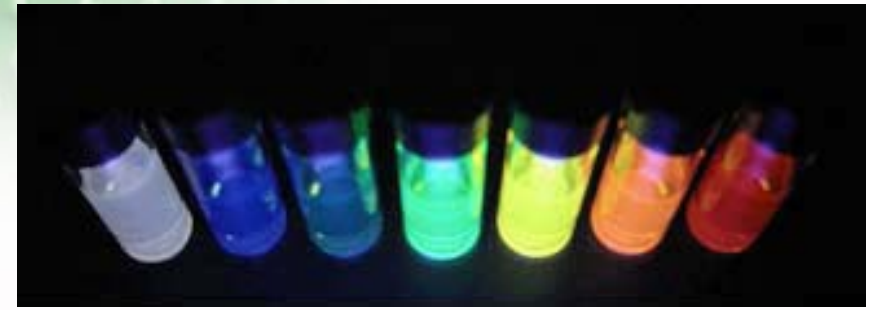
Polymers

- Multiple functions
  - Tissue targeting
    - Tumor-specific binding
  - Sensing or imaging capability
    - Improved sensitivity
    - Multi-modal imaging
  - Non-invasive treatment
    - Therapeutic localized delivery
    - Localized cell kill
    - Lower dose administered
    - Improved side effect profile

Multiplexed Diagnostic Assays

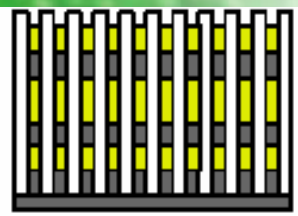
In-vitro Diagnostic
Biomarker
Recognition

Q-dots



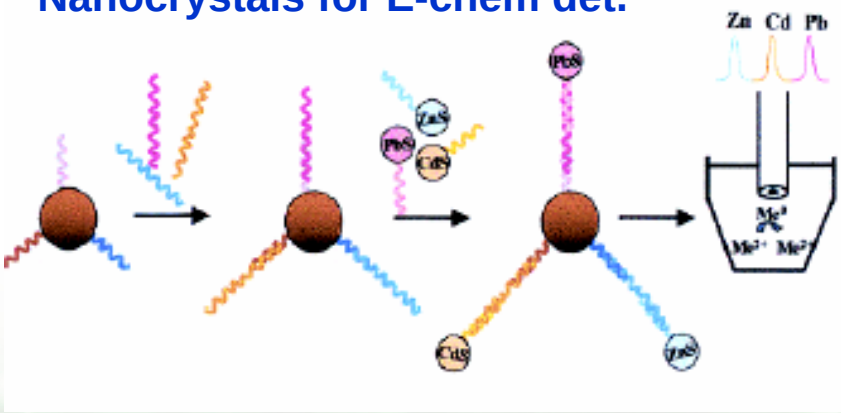
Alivisatos et al.

Nanorods



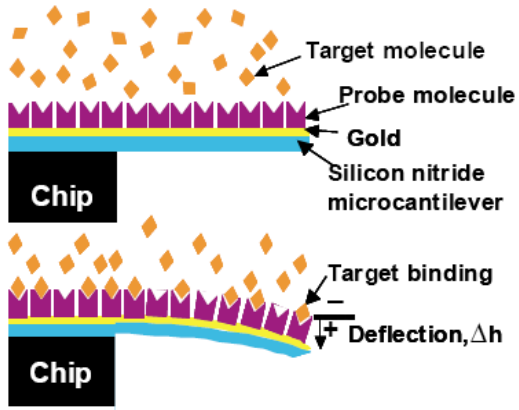
Nicewarner-Pena et al., Science 294, 137 (2001)

Nanocrystals for E-chem det.



J. Wang, Analytica Chimica Acta 500 (2003) 247

Cantilevers

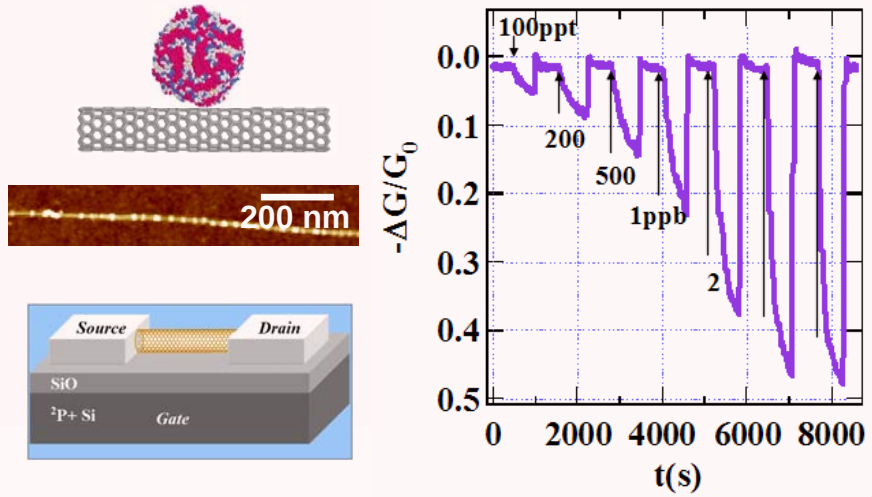


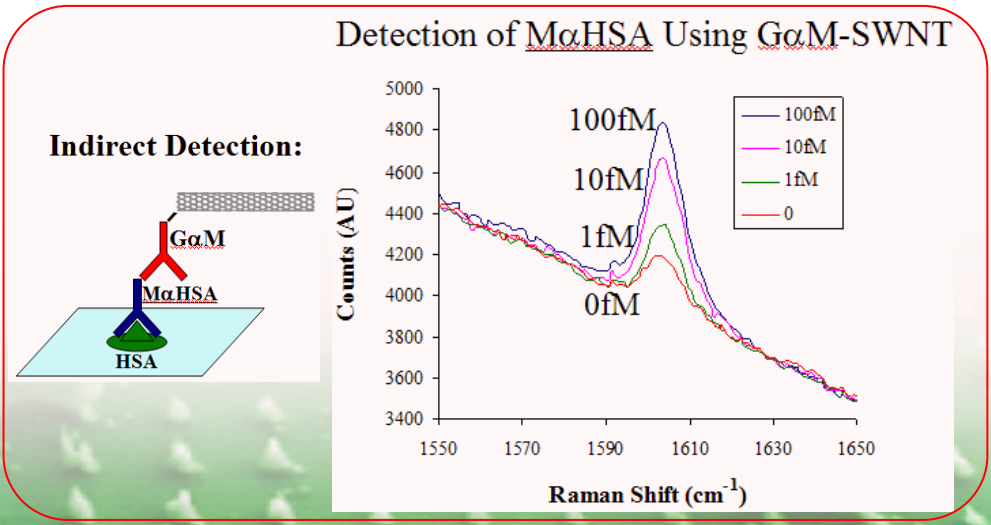
G. Wu and A. Majumdar, *Nature Biotech* 19, 856 (2001)

Single-Walled Carbon Nanotubes in Biological Applications

NCI Alliance for Nanotechnology in Cancer

- **Bio events ➔ electrical signals**
  - Single tube detects ***parts-per-billion*** (NO_2)
  - Extreme surface/volume ratio
  - Protein binding affects electrical property of nanotubes
  - Label-free, electronic readout
- **Sensitive, specific, and multiplex detections of biological molecules**
  - Unusually bright as Raman-labels: ***~10fM sensitivity***
  - Near single molecule detection
  - No need for amplification steps
  - No interfering background
  - Stable signal, no quenching





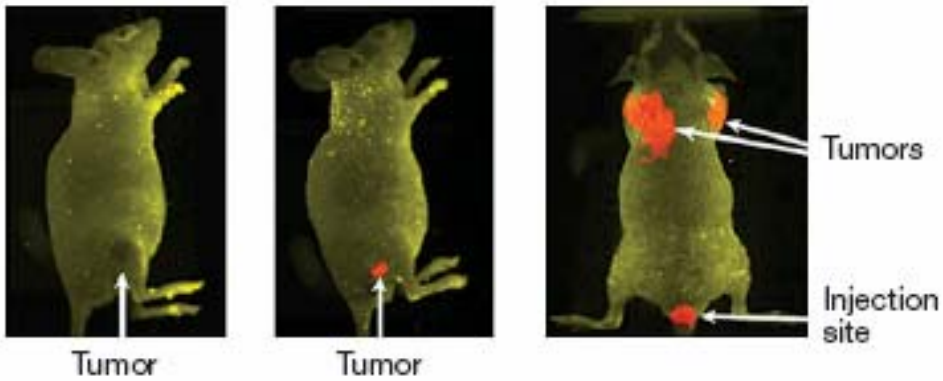
Hongjie Dai, *Stanford CCNE*

Quantum Dots for In-vivo Imaging

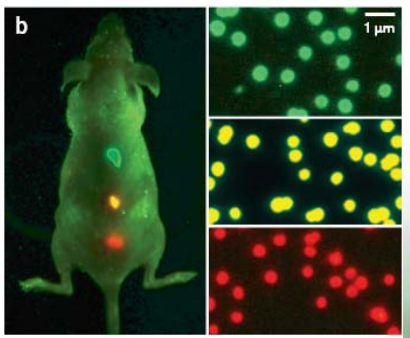
In-vivo Diagnostic
Imaging of Tumor Tissue

Gao and Nie, Nature Biotech 22, 969 (2004)

In vivo fluorescence images of tumor using QD probes

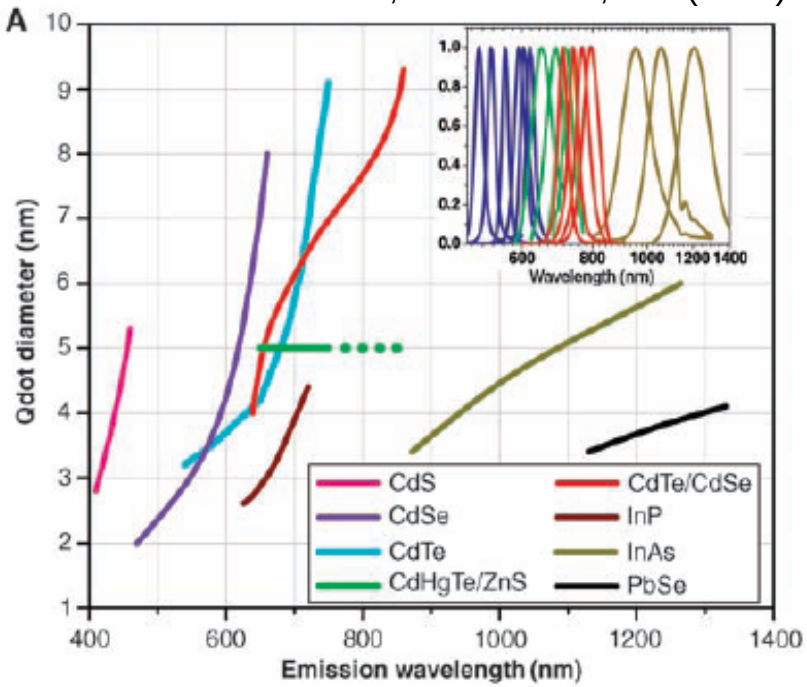


- **Human prostate cancer growing in nude mice**
- **QDs functionalized with PSMA**



Multi-color imaging using the same excitation source

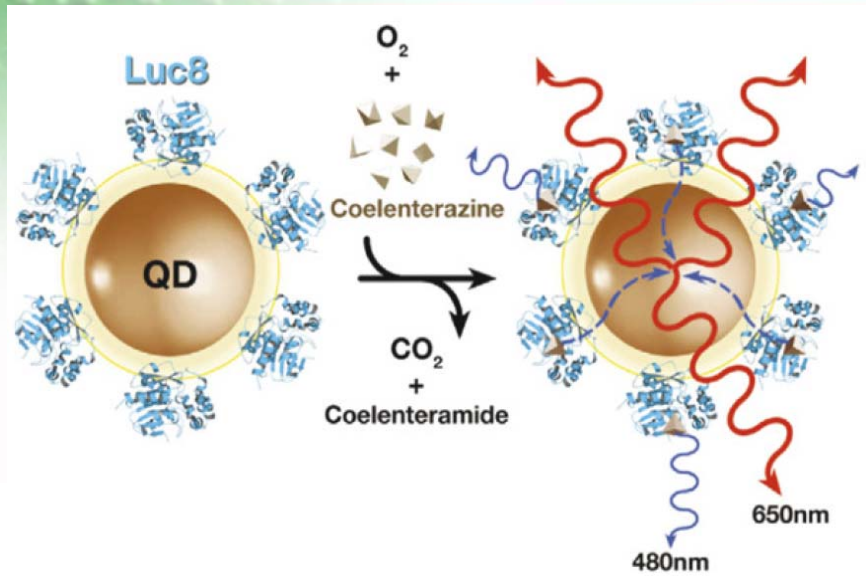
Michalet and Gambhir, Science 307, 538 (2005)

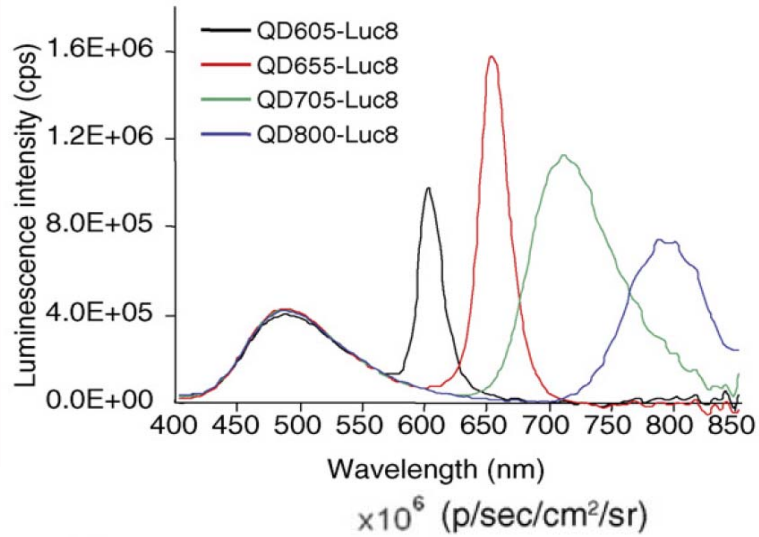


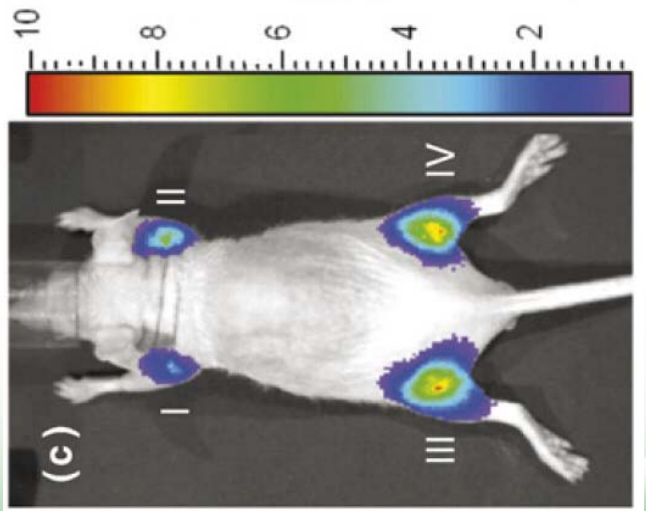
- **Wide range of wavelength coverage using different materials**

Novel Quantum Dots That Do Not Require External Illumination

NCI Alliance for Nanotechnology in Cancer







- Quantum dots conjugated with fluorescent proteins bioluminesce in response to an enzyme-catalyzed reaction
- Bioluminescence resonance energy transfer (BRET) is shown for the first time with quantum dots
- Blood does not interfere with quantum dot signal

So, Gambhir, Rao et al., Self-illuminating quantum dot conjugates for in vivo imaging,Nat. Biotechnol. 24, 339 (2006)

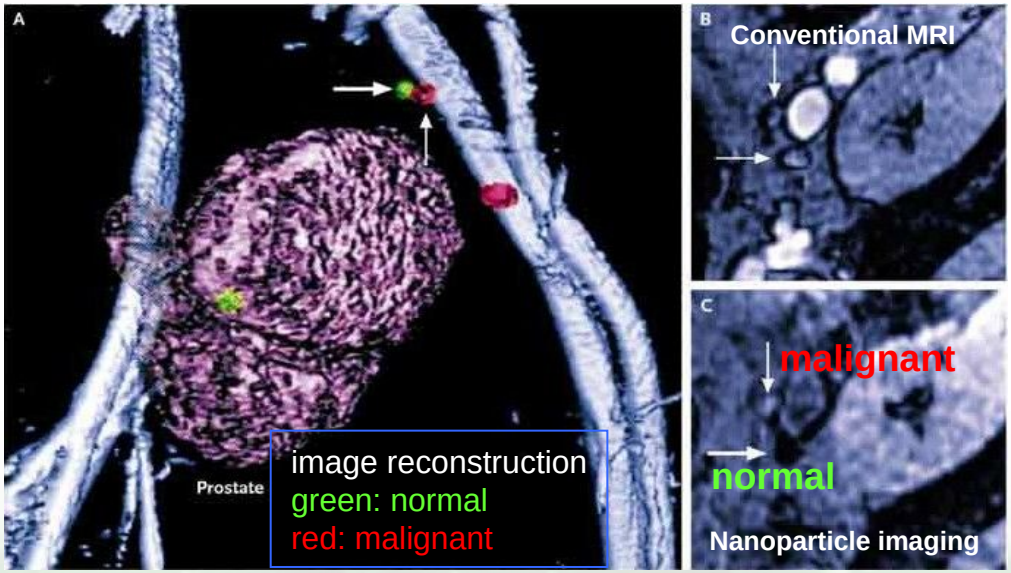
Nanoparticle-based Detection of Lymph Node Metastasis

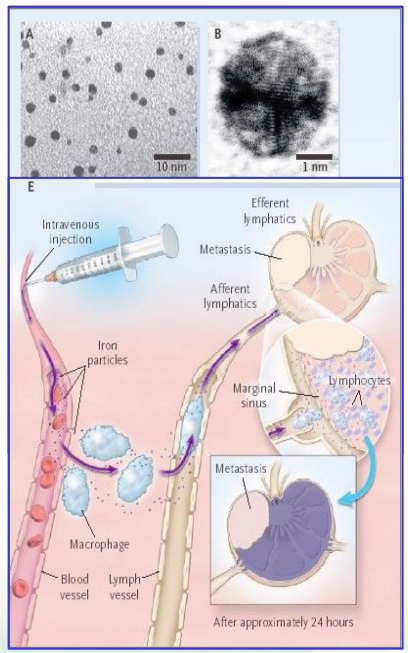
NCI Alliance for Nanotechnology in Cancer

NATIONAL CANCER INSTITUTE

Advanced Magnetics, Inc.

Nanoparticles (dextran-coated iron oxide crystals, Combidex) injected into the circulation travel to the lymph nodes. Metastatic tumors growing in the nodes interfere with particle distribution, and this is detectable by MRI. 80 men undergoing surgery or biopsy for prostate cancer had MRI exams both with and without the nanoparticles before surgery. 33 of the men actually had metastatic lymph nodes. MRI with the particles identified all 33, whereas MRI without the particles missed more than half of them.



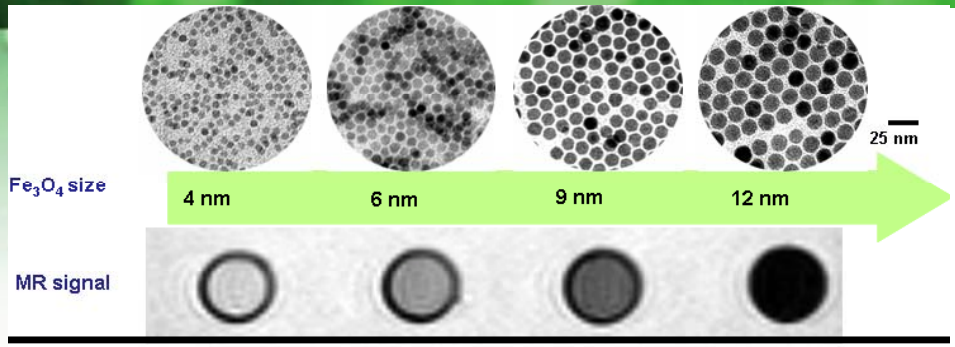


NEJM, 2003, *348:*2491-2499

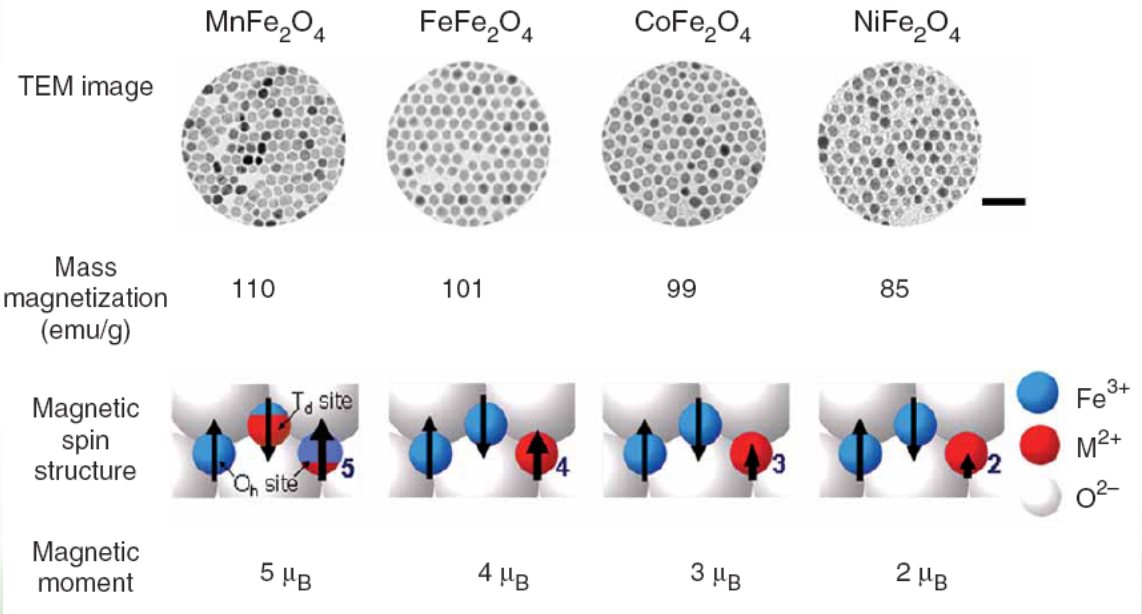
Ralph Weissleder (MGH, Harvard Medical School)
Jean de la Rosette (Netherlands)

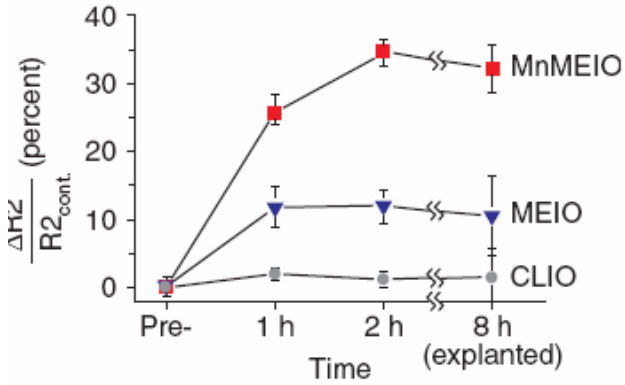
Magnetic Nanoparticles for Ultra-Sensitive Magnetic Resonance Imaging

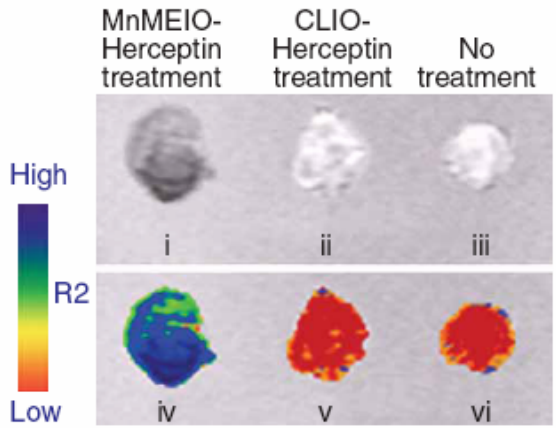
NCI Alliance for Nanotechnology in Cancer



12 nm size of various ferrite nanoparticles







Tom Meade et al, *Northwestern U.*

Cheon et al. Nature Medicine 2007, 13, 95

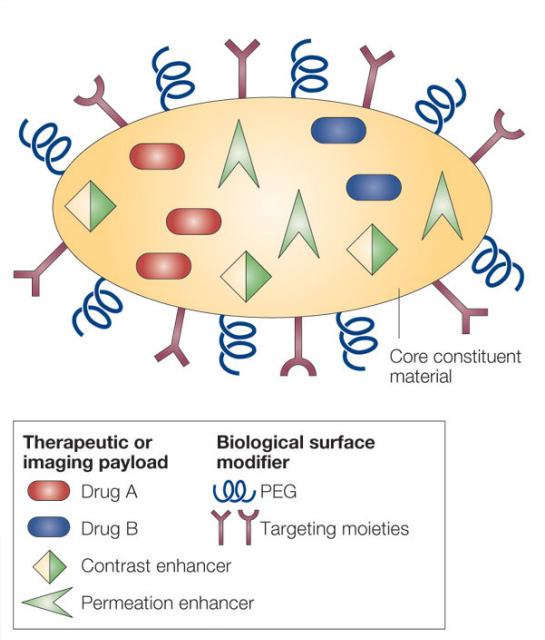
Multi-Functional Nanoparticle-based Therapies

NCI Alliance for Nanotechnology in Cancer

- Multi-functional platforms:
  - Targeting
  - Delivery
  - Reporting, biosensing

→ **In one package**

Free drug formulations do not possess multi-functional characteristics



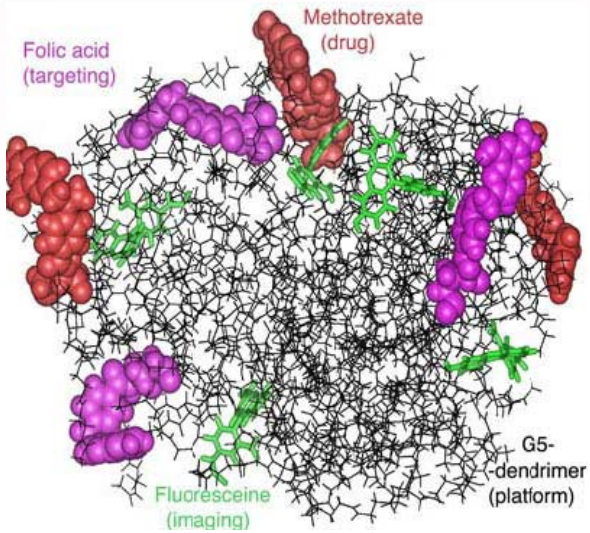
M. Ferrari, *Nature Reviews* 5, 161 (2005)

First generation of nano-delivered drugs (no targeting) approved by FDA – Abraxane®

Nanoparticle-based Therapies: Different Approaches

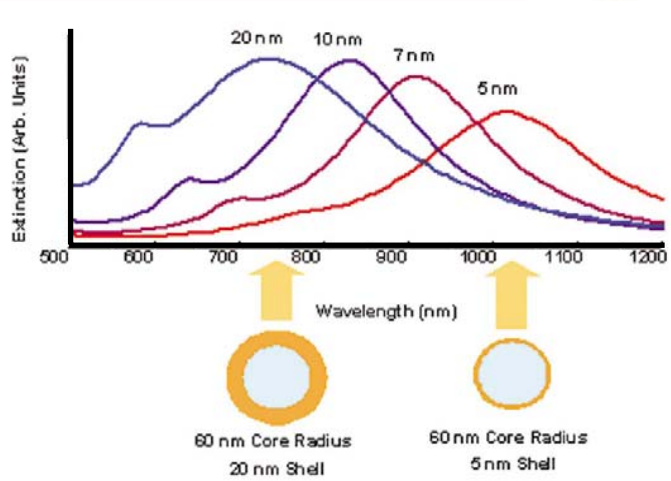
NCI Alliance for Nanotechnology in Cancer

Dendrimers:
Targeted delivery of methotrexate



J. Baker, et al., Cancer Res. 65, 5317 (2005)

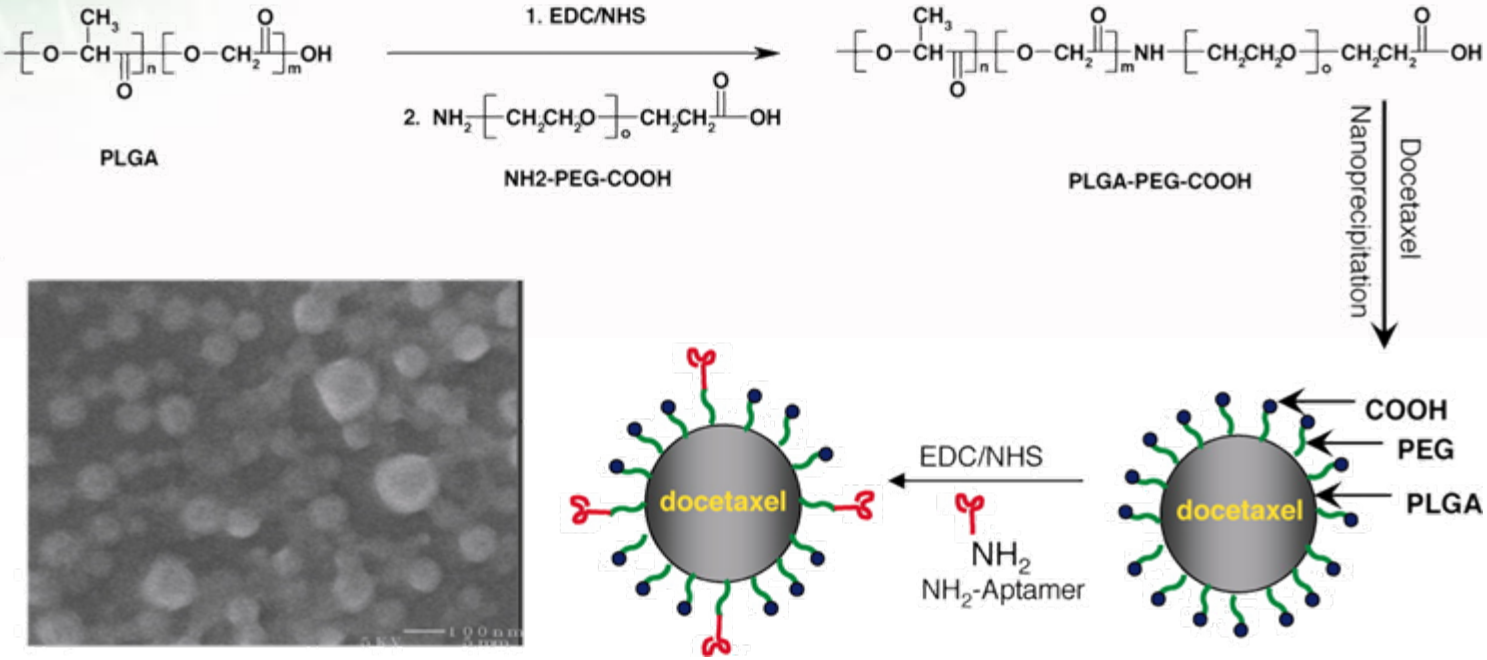
Nanoshells:
Photothermal therapy



N. Halas, J. West et al,
Ann Biomed Eng. 34, 15 (2006)

Docetaxel-Encapsulated PLGA Nanoparticle-Aptamer Conjugates

NCI Alliance for Nanotechnology in Cancer



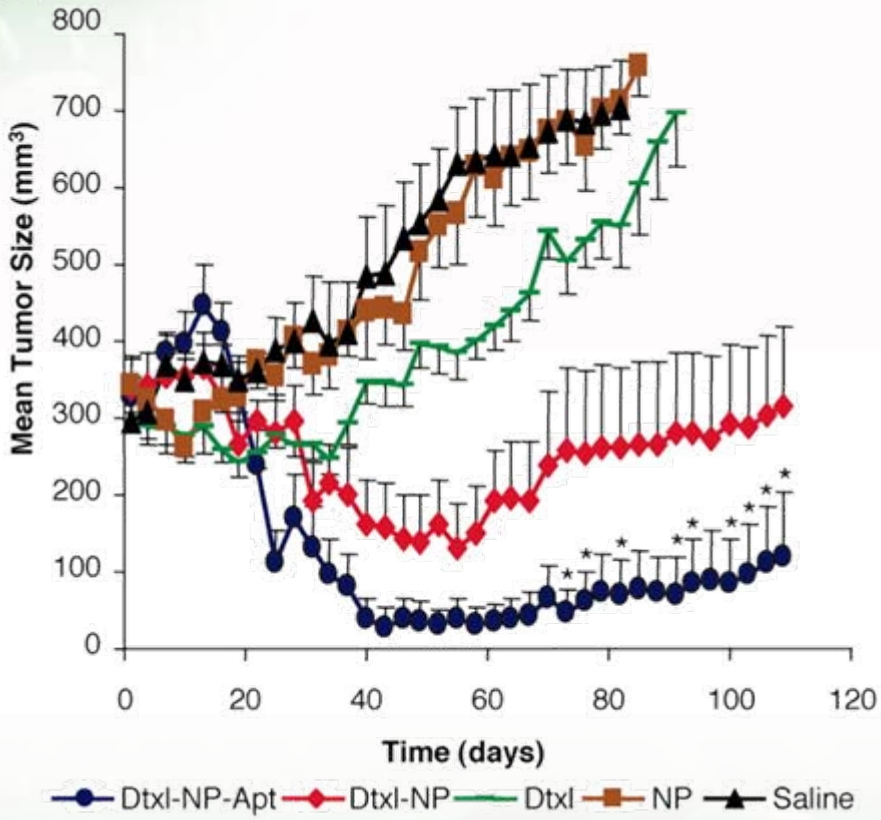
Aptamers are non-immunogenic chemically processed DNA or RNA oligonucleotides that bind to antigen with high affinity and specificity; nanopaticle-aptamer conjugates have been developed for Prostate Specific Membrane Antigen (PSMA)

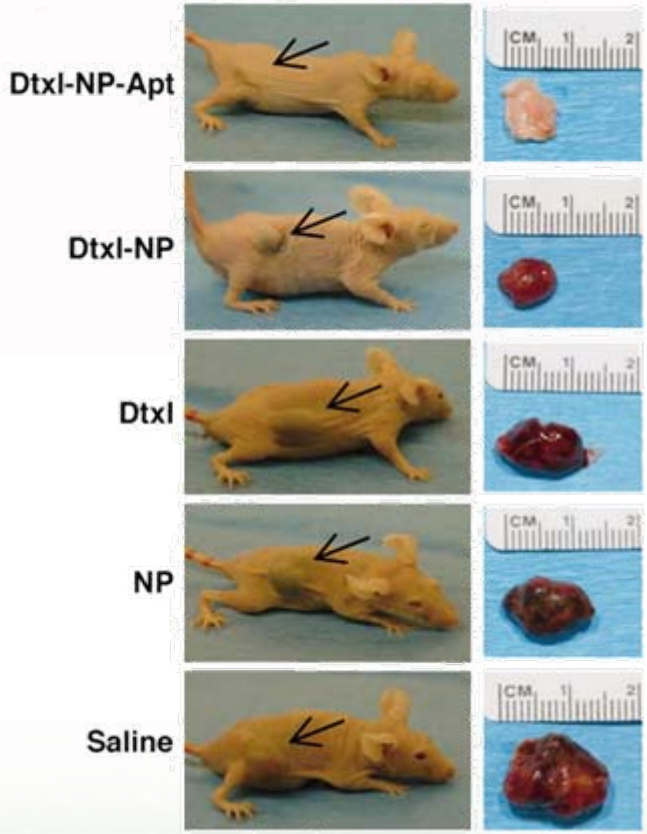
Farokhzad, Cheng, Langer et al., Targeted nanoparticle-aptamer bioconjugates for cancer chemotherapy in vivo, Proc Natl Acad Sci 103, 6315 (2006)

NP-Apt Conjugates: Comparative Efficacy Study

NCI Alliance for Nanotechnology in Cancer

NP-Apt conjugates show greater efficacy in a xenograft mouse model than non-targeted nanoparticles



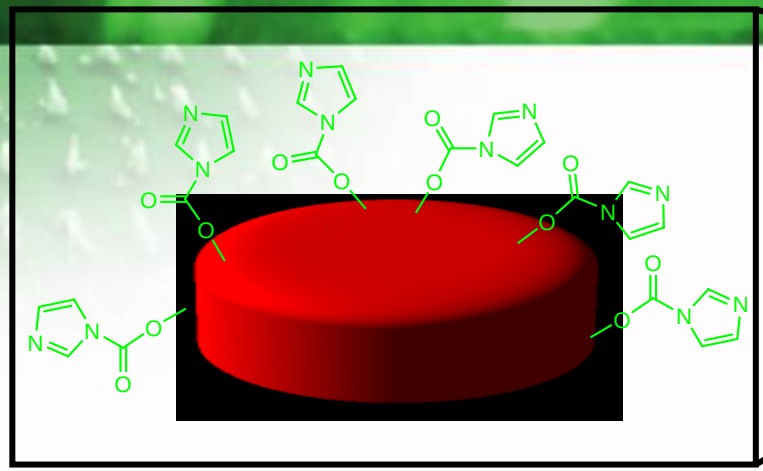


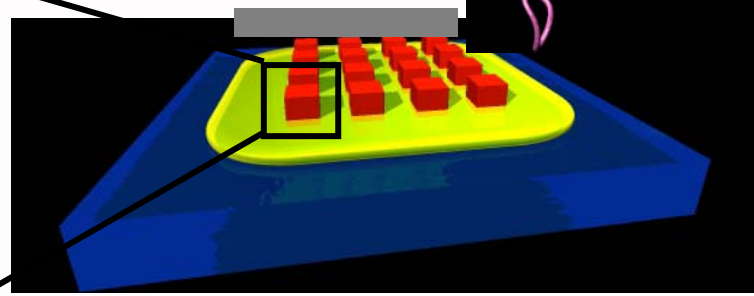
LNCaP s.c. xenograft nude mouse model of PCa; single intratumoral injection (day 0)

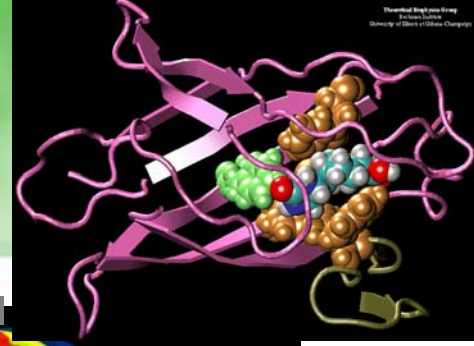
PRINT™ Particles:

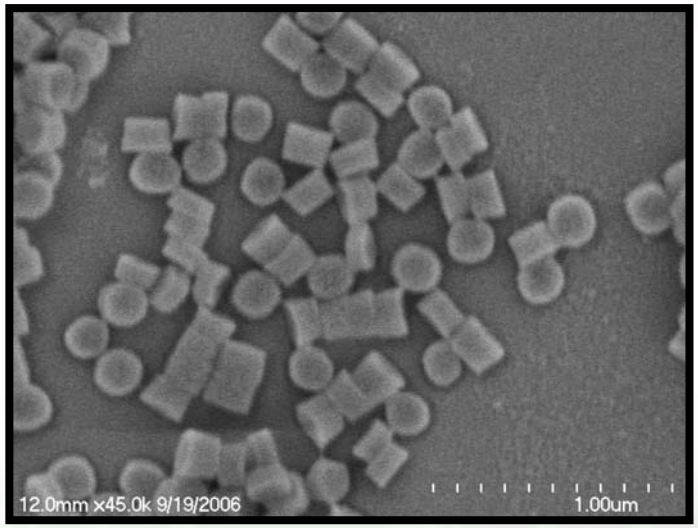
CDI-Activated PEG for Functional Targeting

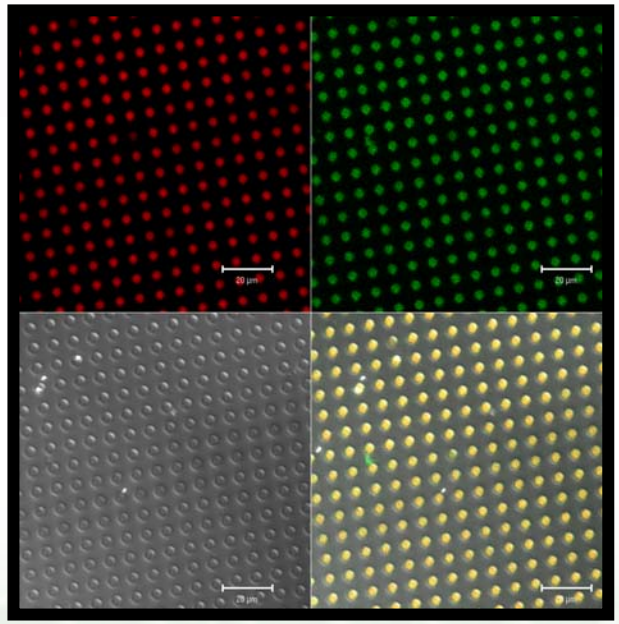
Joe DeSimone, UNC











Multiplexed Delivery of Targeted Anticancer Agents

Nanotechnology: Environmental and Safety Considerations

NCI Alliance for Nanotechnology in Cancer

- Hazard identification
  - *In vitro* toxicity
  - Acute *in vivo* toxicity
  - Subchronic/chronic toxicity
  - Route of exposure
- Dose response
  - External dose
  - Internal dose
  - Biologically effective dose
- Exposure assessment
  - Human exposure

Nanomaterials production

National Toxicology Program

NIEHS

Chronic exposure of the worker

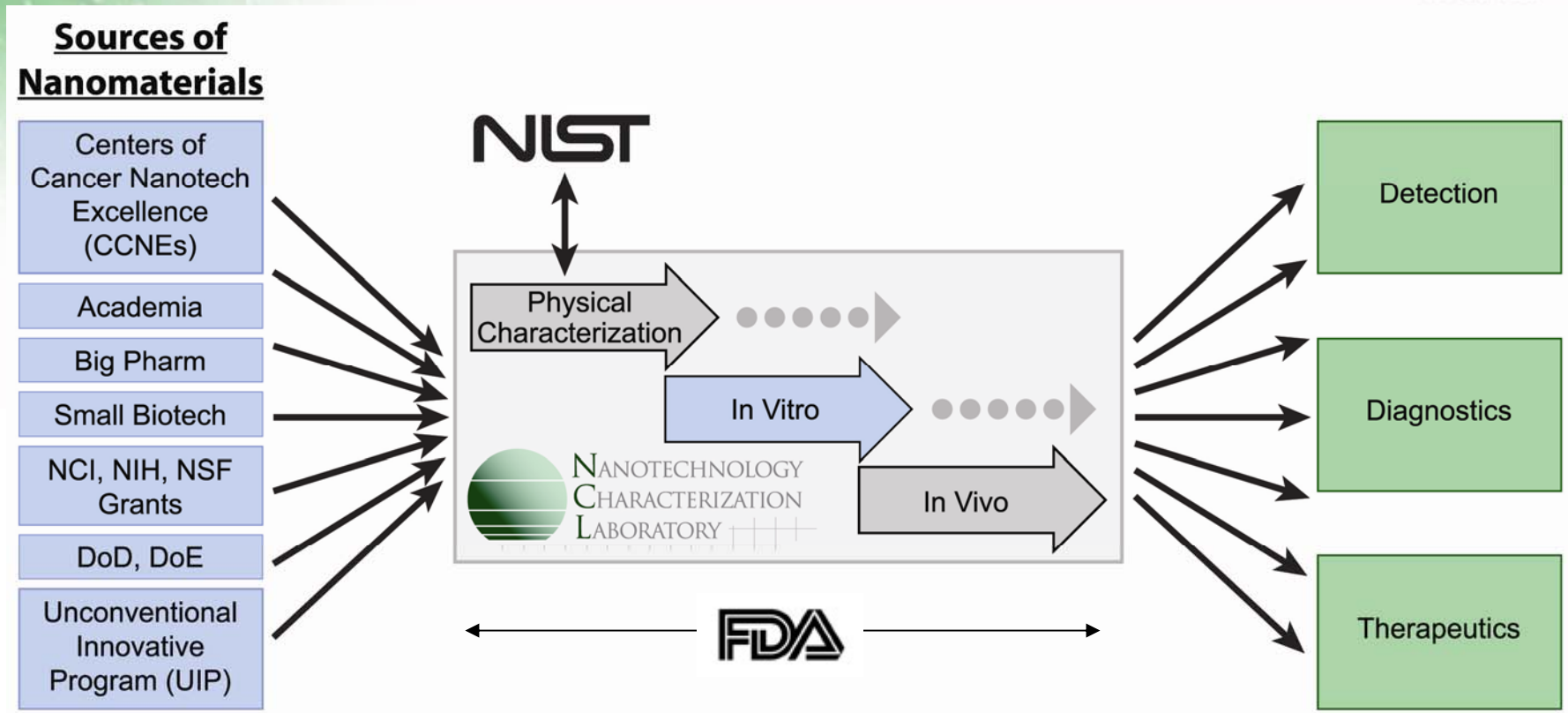
Nanomaterials use for biomedical applications

Nanotechnology Characterization Laboratory

Preclinical studies

NCL Concept of Operations

NCI Alliance for Nanotechnology in Cancer



NCL is a formal collaboration between NCI, FDA and NIST

Current Status

NCI Alliance for Nanotechnology in Cancer

- Development of new diagnostic and therapeutic platforms is at different levels of maturity
- Two drugs approved by FDA: 1) Abraxane – paclitaxel bound to albumin (Abraxis Bioscience) and 2) Doxil – liposome encapsulated doxorubicin
- Common scheme for therapeutics – use existing drugs and adapt them to nano-based delivery platform
- In-vitro diagnostic tools to evaluate clinical samples
- Several companies (2-5) ready to file IND within next 12 months

Future prospects

NCI Alliance for Nanotechnology in Cancer

- Broader engagement of oncologists in the technology development is needed
- Are multi-functional (target, reporter, and therapy) solutions practical or too complex?
- Can the development of new drugs benefit from nanotechnology?
  - New screening methods
  - New formulations?
- Combination of in-vivo diagnosis and tailored therapy

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