



NATIONAL  
CANCER  
INSTITUTE

NCI Alliance for  
**Nanotechnology**  
in Cancer

The National Academies  
*Critical National Needs in New Technologies: Opportunities for the  
Technology Innovation Program*

# Nanotechnology: Transformational Technologies for Cancer and Other Diseases

*24 April 2008*

**Anna D. Barker, Ph. D.**  
Deputy Director  
National Cancer Institute

# Catalyzing – Accelerating Progress Toward Molecular-Based Cancer Medicine

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**Why nanotechnology for cancer?**



**Why Nano is Promising for Cancer**



**The NCI Alliance for Nanotechnology in Cancer - Current Status**



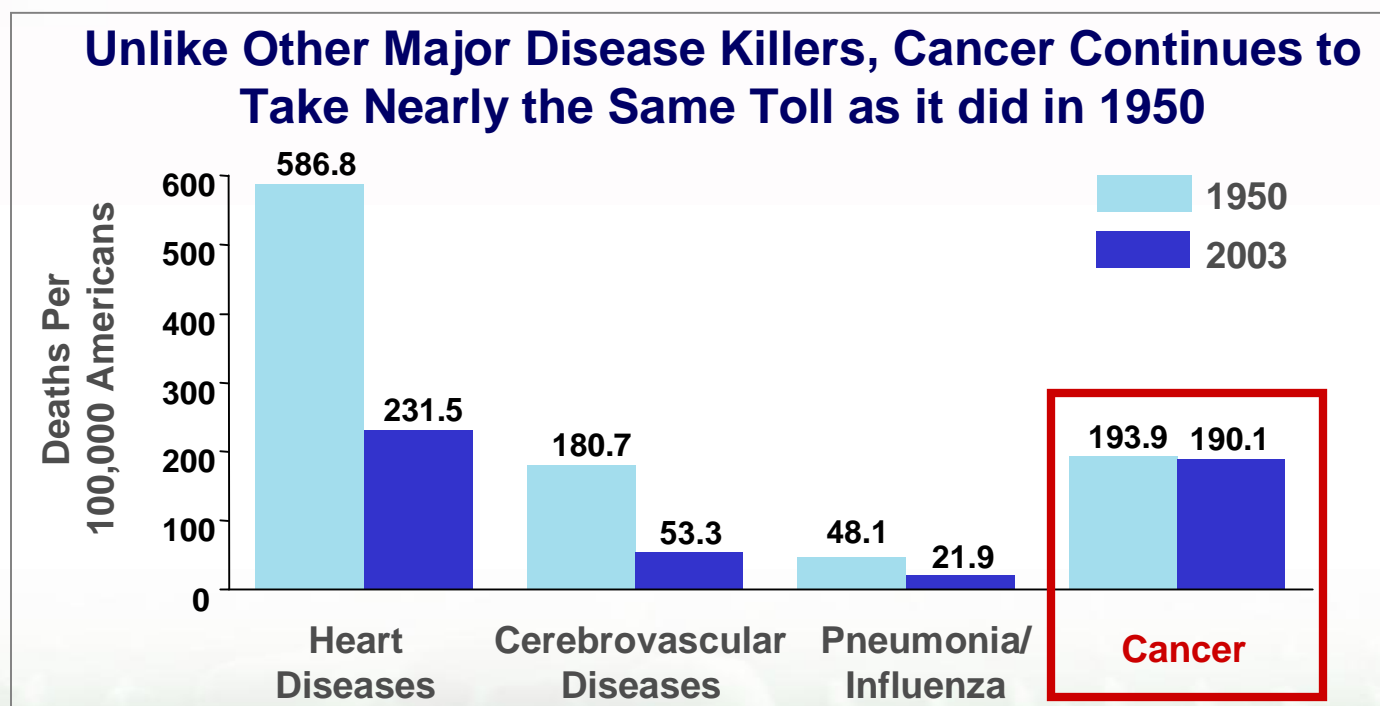
***Examples of the Science***



# Why Cancer? Mind-Numbing Statistics

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- 564,830 Americans died of cancer in 2005
- 1,399,790 Americans will be diagnosed with cancer this year
- \$209.9 billion in 2005 for cancer healthcare costs
- Numbers of new cancer cases will approach 2 million by 2025 (Aging of the baby boomers)

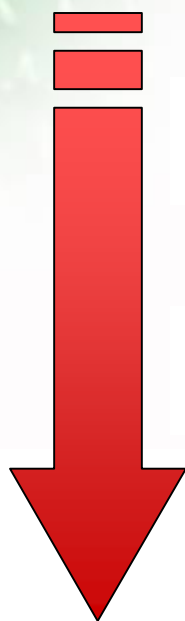


Source for 2006 deaths and diagnoses: American Cancer Society (ACS) 2006 Cancer Facts & Figures; Atlanta, Georgia  
Source for 2003 age-adjusted death rate: National Center for Health Statistics, U.S. Department of Health and Human Services, NCHS Public-use file for 2003 deaths.



# Why Cancer: A Major Barrier - Cancer's Complexity

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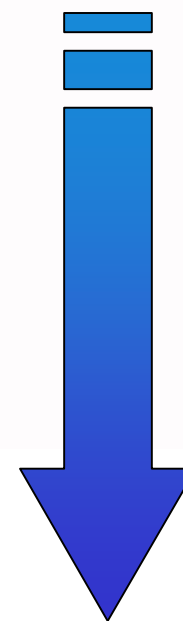


**Increasing  
layers of  
complexity**

**Genomics**

**Proteomics**

**Systems Biology**

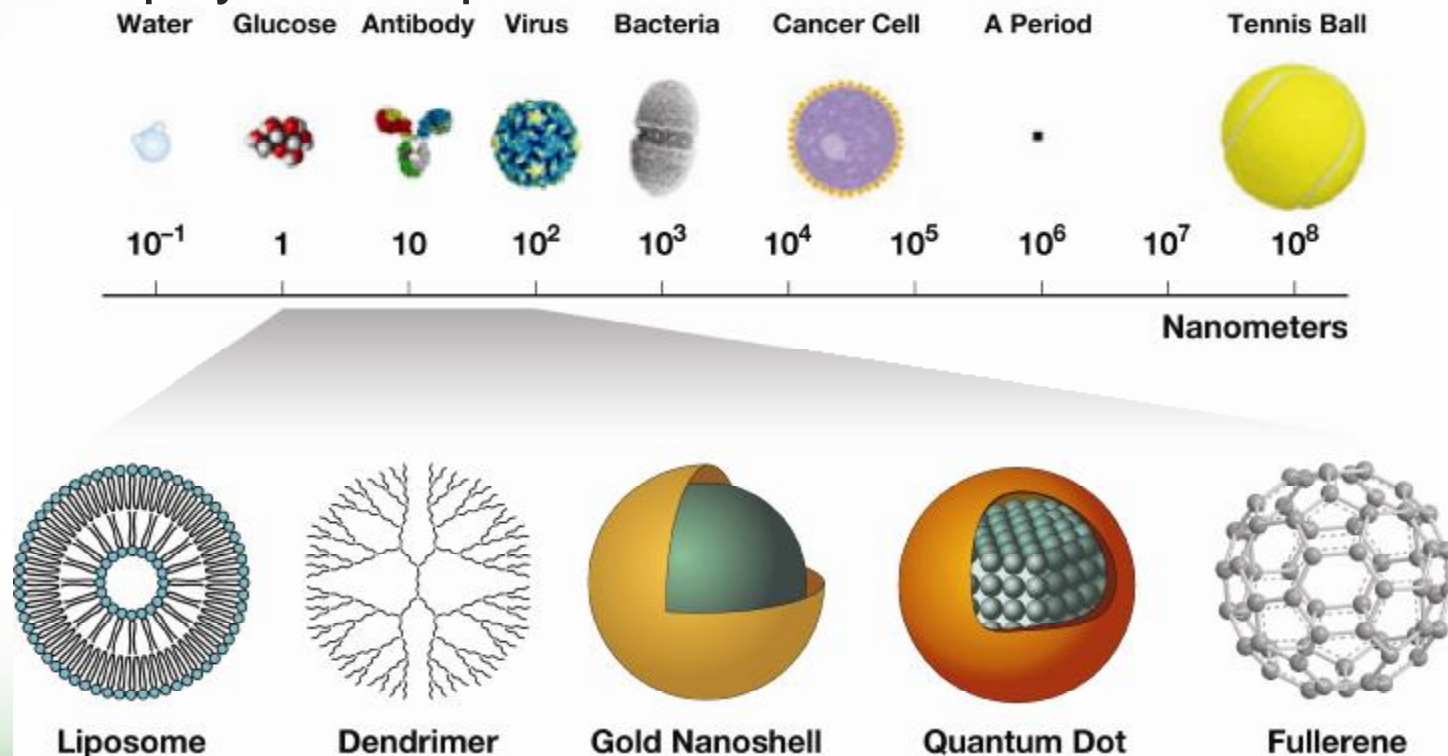


**Decreasing  
Technological &  
Methodological  
Capabilities/  
Reagents/Systems**

# Nanotechnology: New Ways to Interrogate the Complexity and and Specifically Intervene

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Varying dimensions and constructs lead to wide array of functional elements – physics at the nanoscale is complex – classic physics....quantum mechanics



# Nanotechnology and the Future of Cancer

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**Nanotechnology is a “disruptive technology” that promises to enable the transition of molecular-based science into the clinic – creating a new generation of diagnostics, therapeutics and preventives for cancer**

Controlling matter in the range of 1-100 nanometers

- |                            |   |
|----------------------------|---|
| § <b>Early detection –</b> | <b>highly sensitive and specific sensors</b>                            |
| § <b>In-vivo imaging –</b> | <b>new contrast agents, localization</b>                                |
| § <b>Therapeutics –</b>    | <b>local, on-particle delivery, targeted, monitoring, multi-plexing</b> |
| § <b>Prevention -</b>      | <b>detect early genomic/proteomic changes</b>                           |





# National Cancer Institute's Nanotechnology Initiative for Cancer

# Technology and its Impact on the Disease

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- **Devices to diagnose the disease**  
↓
- **Devices to treat the disease**  
↓
- **Devices to monitor the disease in post-treatment stage**  
.....
- **Tools and devices to understand the processes behind the development and spread of the disease**  
↓
- **Devices to reverse/alter the progress of the disease**



# NCI Alliance for Nanotechnology in Cancer – Funded in 2005

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- Multi-Year planning process, extramural meetings and workshops – dedicated NCI and expert nanotechnology leadership\*
  - Focus on multi-disciplinary teams, addressing key problems in oncology, accelerating progress of nano-products to the clinic
- \$144.3M initiative



# Hallmarks of the Alliance

NCI Alliance for  
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- Requires academic and commercial partnerships for each supported Alliance project
- Commits major funding that leverages existing infrastructure
- Establishes training programs
- Coordinates with other Federal agencies to leverage NCI funds and creates synergies
- Pre-qualifies new materials and informs standards through the Nanotechnology Characterization Laboratory
- Reduces the risk of investment in new products
- **Leverages effective input and outreach through patient advocacy communities**

# Major Programs of the Alliance

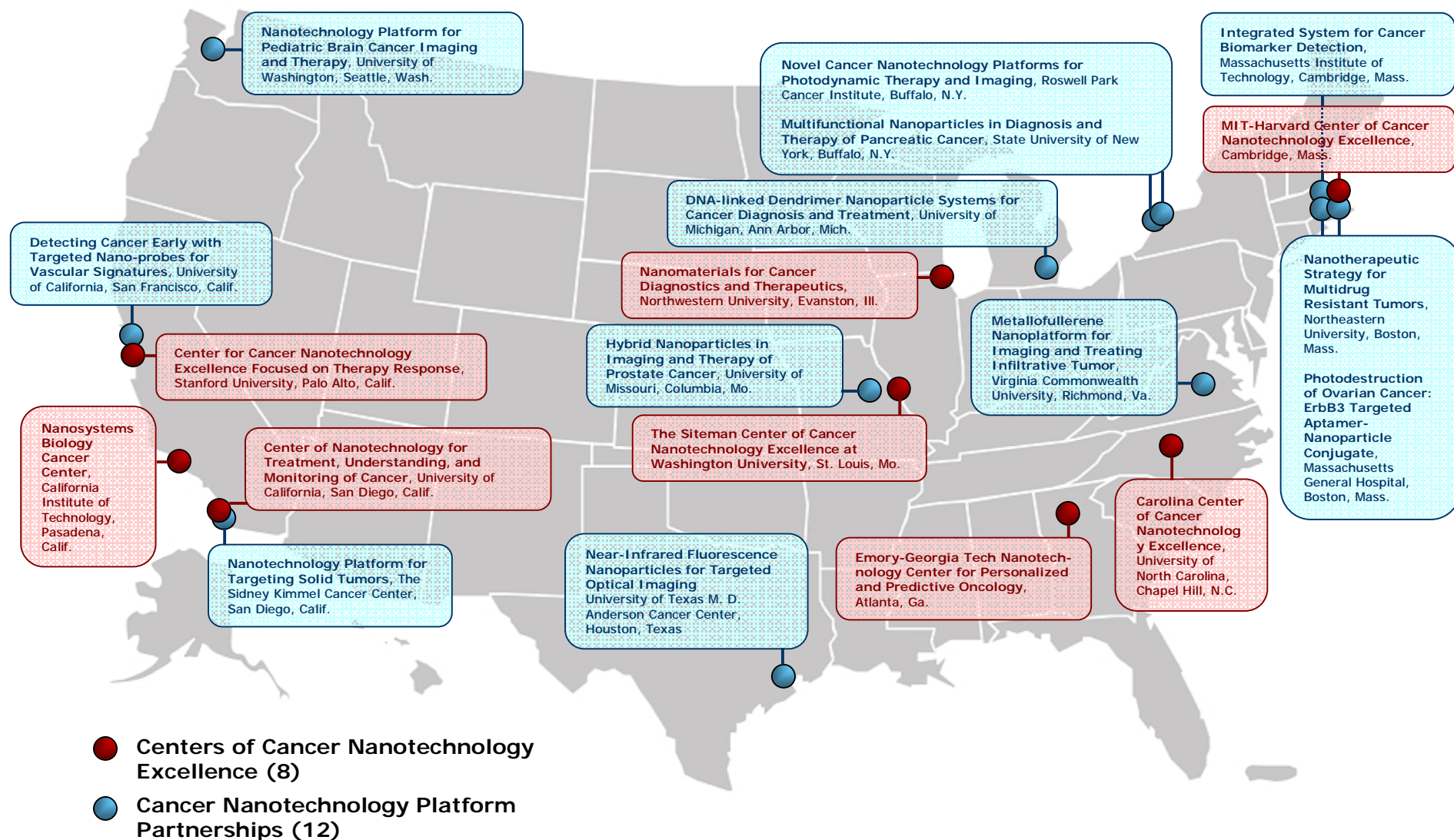
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- 1** Centers of Cancer Nanotechnology Excellence
- 2** Nanotechnology Platforms for Cancer Research
- 3** Multidisciplinary Research Training and Team Development
  - Fellowships in Cancer Nanotechnology Research
  - Interagency Collaborations
- 4** Nanotechnology Characterization Laboratory



# NCI's Alliance for Nanotechnology in Cancer

NCI Alliance for  
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# NCI-NSF Nanobiotechnology Collaboration

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**Building Leadership for the  
Nanotechnology Workforce of  
Tomorrow**, University of  
Washington, Seattle, WA –  
*Marjorie Olmstead, PI*

**Nanomaterial Science and  
Technology**, Northeastern  
University, Boston, MA –  
*Srinivas Sridhar, PI*

**Integrative Nanoscience  
and Microsystems**,  
University of New Mexico,  
Albuquerque, NM –  
*Diana Huffaker, PI*

**NanoPharmaceutical  
Engineering and  
Science**, Rutgers  
University, New  
Brunswick, NJ –  
*Fernando Muzzio, PI*

● IGERT Training Grants (4)

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# Nanotechnology Characterization Laboratory (NCL)

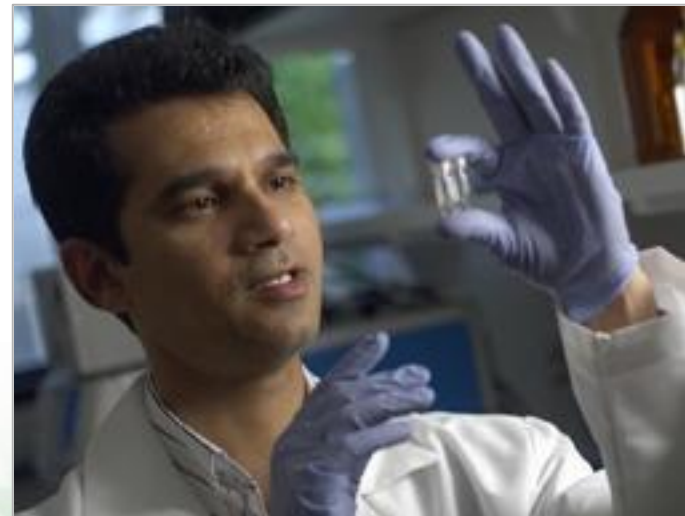
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- NCL Role:
  - Interface with CCNEs, individual investigators, NIST and FDA to develop standards and characterization data for nanoscale materials
  - Perform preclinical toxicology, pharmacology, and efficacy testing of nanoscale devices
  - Formulate and validate protocols for physical, *in vitro*, and ADME/tox characterization of nanoparticles

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FDA

NIST





# Alliance Involves Interagency Collaborations

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**NIST**

- **Standards/Precision Measurement Capabilities**



- **Training**
- **Dissemination of Results**



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INITIATIVE

- **Public Interface**
- **Interpret Data on Environment, Health and Safety**



- **Shared Data and Platforms**

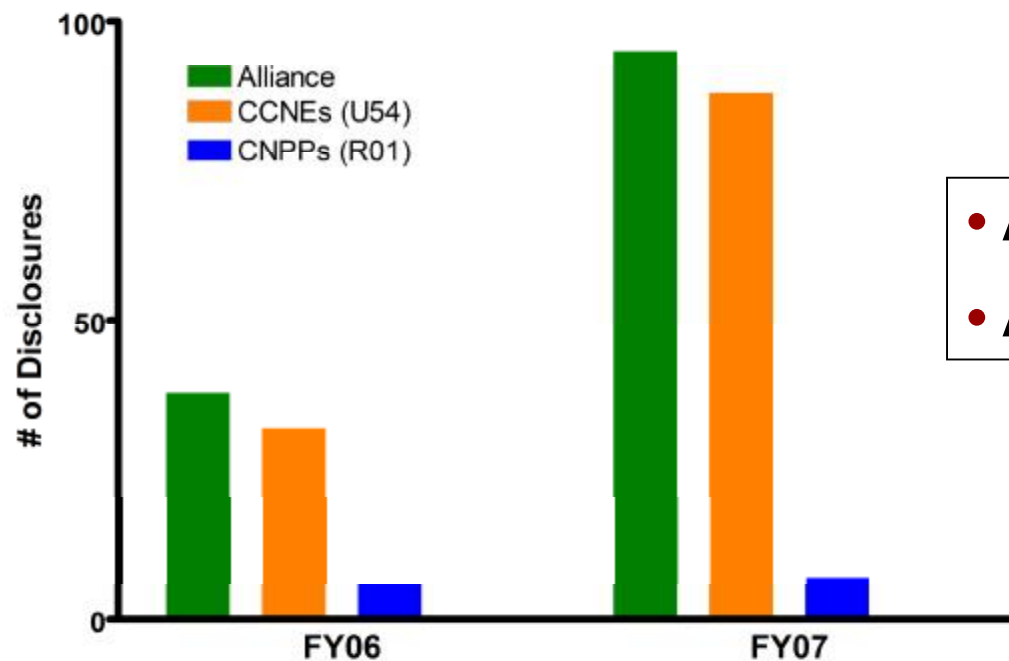


Two Years Later: Some Snapshots  
from the Alliance

# Patent Applications, Technology Transfer, New Companies

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**29 Companies Formed to date  
By Nano-Alliance Members**



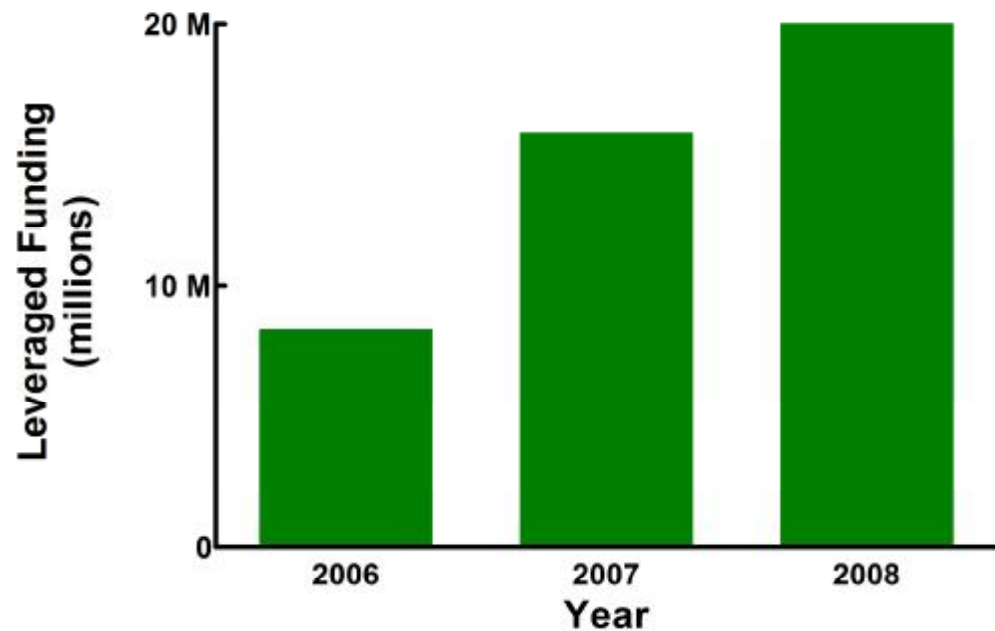
- After 1<sup>st</sup> year – 38 disclosures
- After 2<sup>nd</sup> year – 133 disclosures



# Leveraged Funding

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- Over \$80 million of new research funds (accumulative amount for period of next five years)
  - Diversified portfolio from federal, state, and foundation sources
- 
- \$100 M donation to MIT for new cancer center
  - \$25-50 M from state of N. Carolina towards cancer research





# Developing and Delivering A New Generation of Cancer Nanotherapies

# Nano-therapeutics

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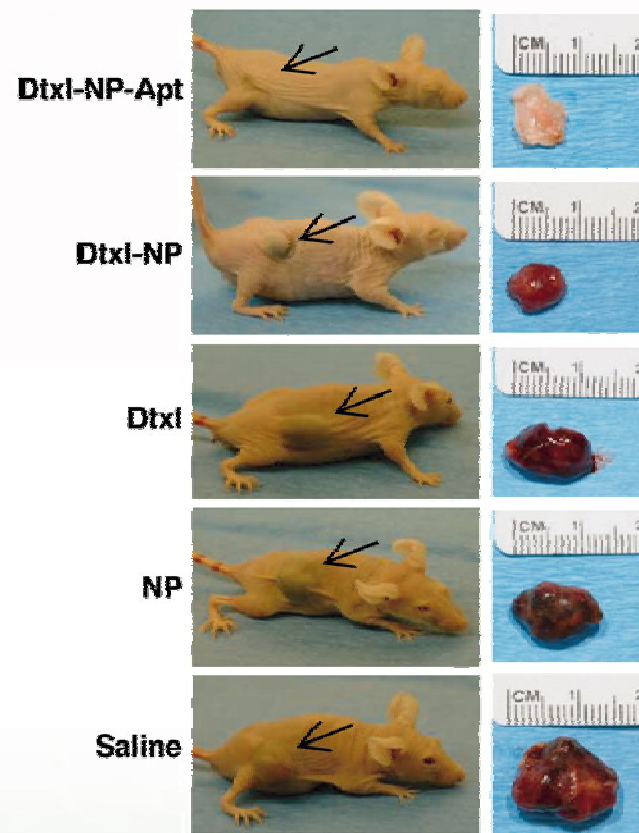
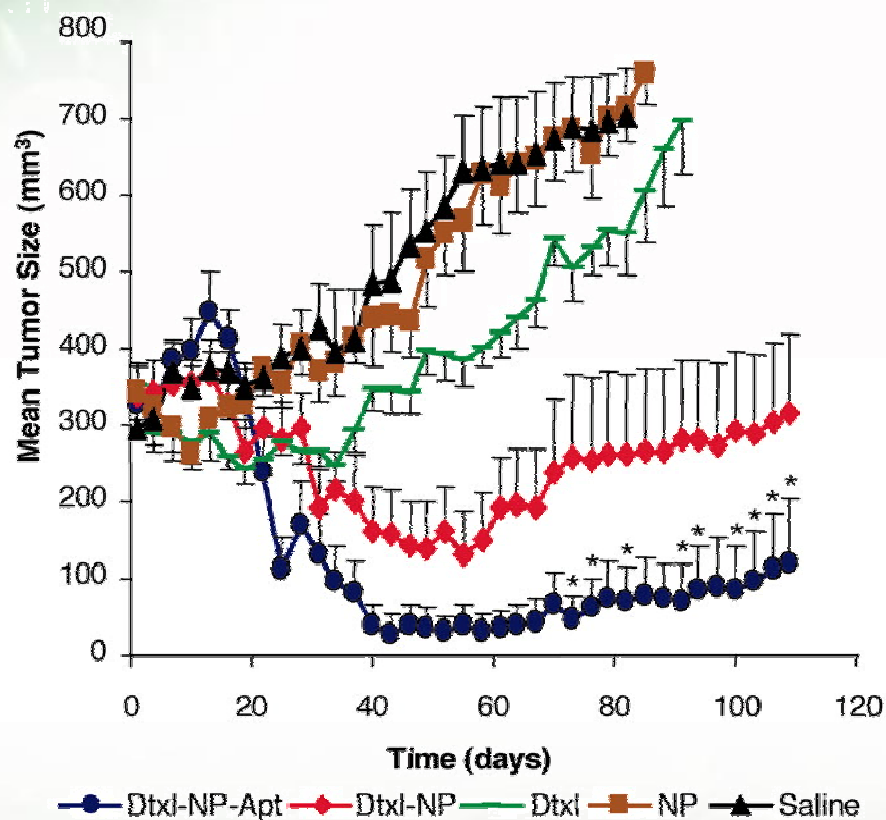
- Two drugs approved by FDA: 1) Abraxane – paclitaxel bound to albumin (Abraxis Bioscience) and 2) Doxil – liposome encapsulated doxorubicin
- Handful of clinical trials
- Common scheme for therapeutics – use existing drugs and adapt them to nano-based delivery platform
- Several companies (2-5) ready to file IND within next 12 months



# Docetaxel-Encapsulated PLGA Nanoparticle-Aptamer Conjugates

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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)

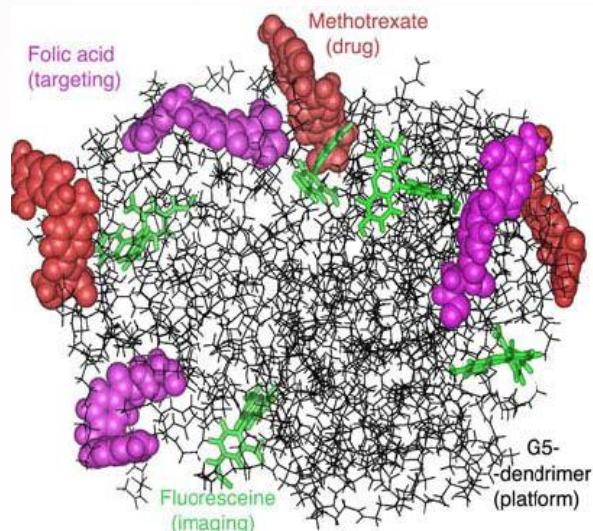
Farokhzad, Cheng, Langer et al.

# Nanoparticle-based Therapies: Different Approaches

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## Dendrimers:

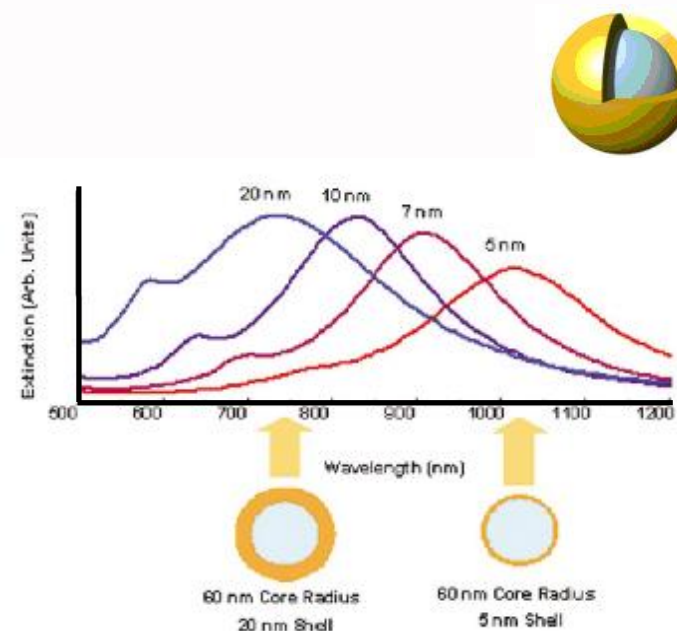
Targeted delivery of methotrexate



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

## Nanoshells:

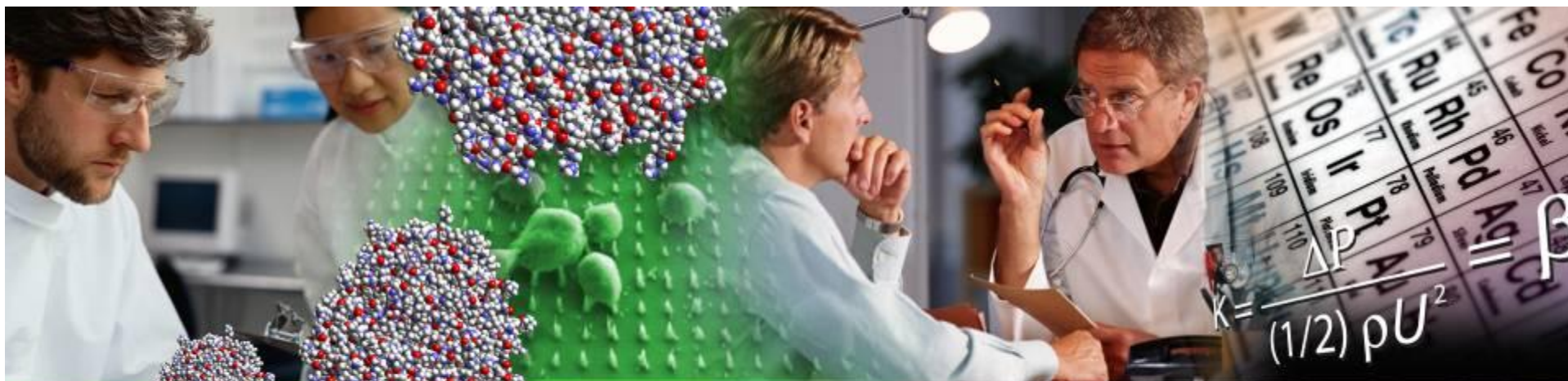
Photothermal therapy



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

Company	Product(s)	Material	Indication	Status	Admin.
Abraxis Bioscience	<b>Abraxane</b>	Albumin-bound paclitaxel	NSC lung cancer, breast, others	<b>Approved</b>	IV
Advanced Magnetix	Combidex	Iron oxide nanoparticles	Tumor imaging	NDA filed	IV
Avidimer	Platform, ATI-001	Targeted dendrimers	Various cancer	Pre-clinical	IV
BIND	Platform technology	Targeted PLGA-PEG nanoparticles	Prostate cancer, others	Pre-clinical	IV
Calando	Targeted siRNA	Cyclodextrin polymers- siRNA	Cancer, others	Pre-clinical	IV
Carbon Nanotechnology	DF1	Dendritic fullerene	Chemoprotection	Pre-clinical	IV
Cytimmune	<b>Aurimune</b>	TNF $\alpha$ -bound colloidal gold	Solid tumors	<b>Phase I</b>	IV
Cytimmune	Auritrol	Taxol and TNF $\alpha$ -bound colloidal gold	Solid tumors	Pre-clinical	IV
Dendritic Nanotechnologies	Dendrimer-Magnevist	PAMAM dendrimer	MRI imaging agent	Pre-clinical	IV
ImaRx Therapeutics	MRX-951	Self-assembling block copolymer	Cancer	Pre-clinical	IV
Insert Therapeutics	<b>Cycloset-camptothecin</b>	Cyclodextrin nanoparticles	Metastatic solid tumors	<b>Phase I</b>	IV
Introgen	<b>INGN-401</b>	Liposome	Metastatic lung cancer	<b>Phase I</b>	IV
Kereos	Platform technology	Perfluorocarbon polymers	Cancer and cardiovascular	Pre-clinical	IV
Liquidia Technologies	Platform technology	PRINT <sup>TM</sup> nanoparticles	Cancer, others	Pre-clinical	IV
Nanospectra Biosciences	<b>AuroLase</b>	Gold nanoshell	Head and neck cancer	<b>Clinical trial - start</b>	IV
OrthoBiotech	<b>Doxil</b>	PEGylated liposome	Metastatic ovarian cancer	<b>Approved</b>	IV
Triton Biosystems	TNT-Anti-Ep-CAM	Polymer-coated iron oxide	Solid tumors	Pre-clinical	IV






# Diagnostics and Imaging: Examples from the NCI Nanotechnology Alliance

# Nanotechnology: Opportunities to Increase Sensitivity – New Molecular Diagnostics/New Generation of Imaging

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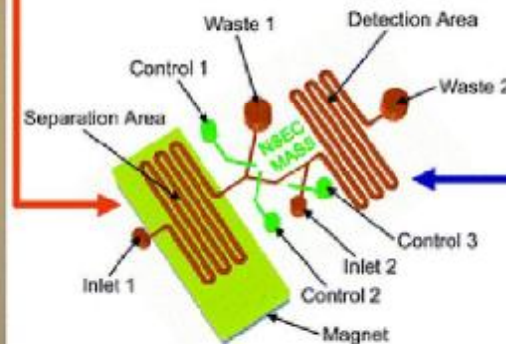
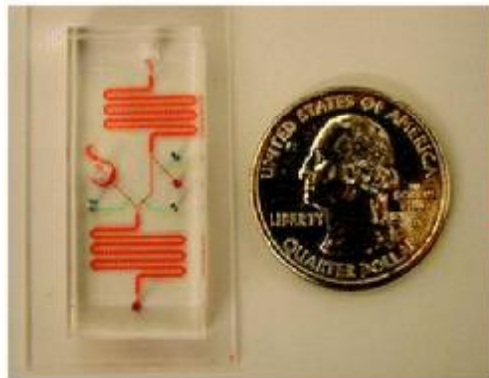
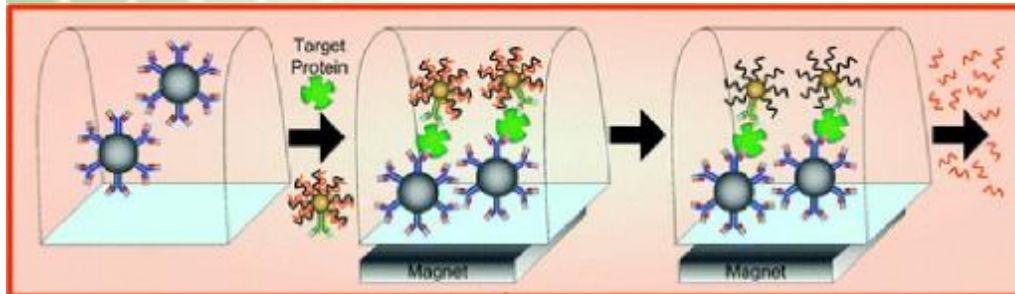
## Biomolecule Detection Technology

	Concentration	Molecule/Drop	Detection/ Targets/Disease
	$10^{-3}$ - Millimolar	Quadrillions	Colorimetric/Enzymatic Chemistry Blood Sugar (Diabetes)
	$10^{-6}$ - Micromolar	Trillions	
	$10^{-9}$ - Nanomolar	Billions	ELISA & Chemiluminescence Troponin, CK-MB, BNP, bHCG
	$10^{-12}$ - Picomolar	Millions	
	$10^{-15}$ - Femtomolar	Thousands	Bio-barcode Technology Cancer: Prostate, Ovarian, Breast Alzheimer's Disease, Mad Cow Pulmonary Disease, Cardiovascular Disease
	$10^{-18}$ - Attomolar	Tens	
	$10^{-21}$ - Zeptomolar	<1	

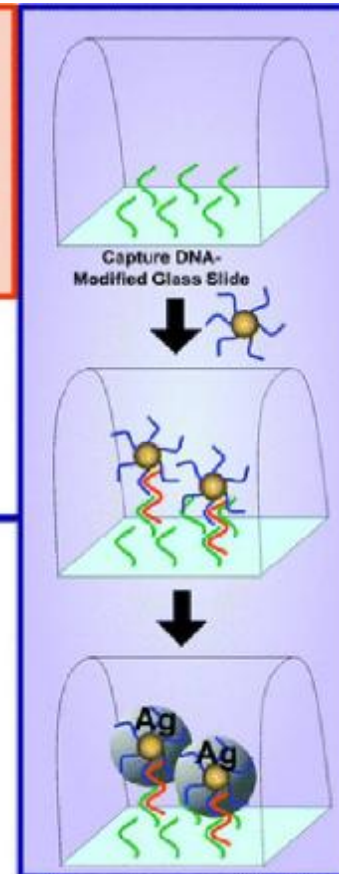


# Problem: Sensitivity to Detect Early Changes in Cancer – (BioBarCode (BBC) Assay Detection)

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 Monoclonal PSA Antibody
  Polyclonal PSA Antibody
  Functionalized Magnetic Particle
  Gold Nanoparticle
  Barcode DNA



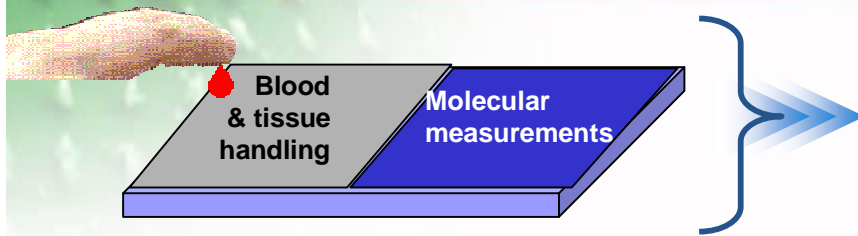
## 'Nano' Added Value

- Use nanoparticles (NP) as tags to target specific protein **AND attach  $10^3 - 10^6$  DNA strands**
- The  $10^3 - 10^6$  DNA strands provide *built-in* signal amplification to each NP.  
**.(Amplification w/o PCR)**
- ***Ultrahigh sensitivity***
- The approach should be applicable targets with known Abs.



# Protein Detection Using Sensitive Silicon Nanowire Technology

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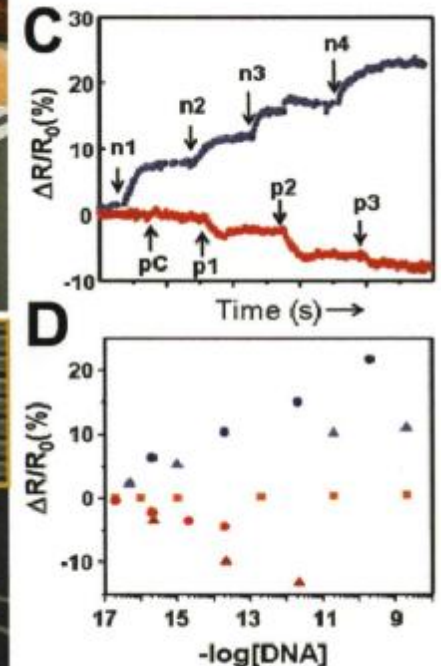
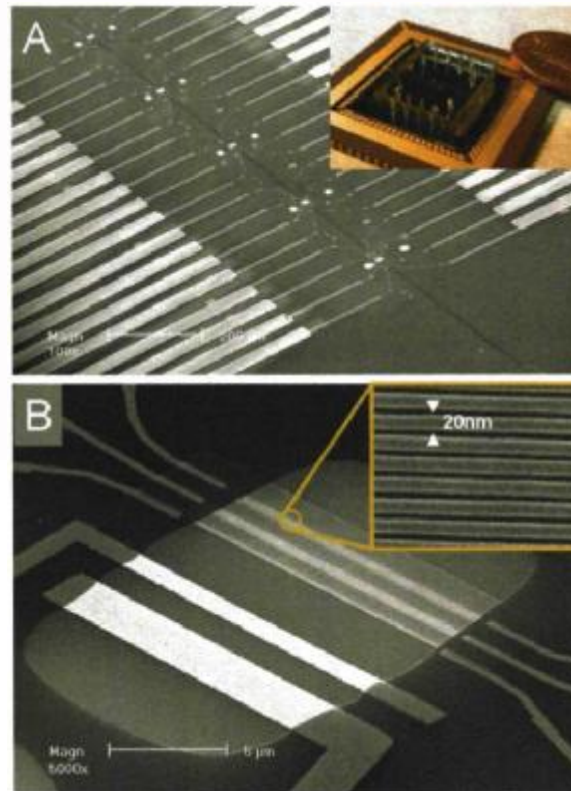


- **Systems biology approach**

- Personalize detection, treatment, and monitoring of cancer

- **Silicon nanowires chips**

- ~**100 attoM** sensitivity and  $10^6$  dynamic range
- Up to **3200** simultaneous measurements can be made
- Tested in serum-like environments



## **Silicon nanowires**

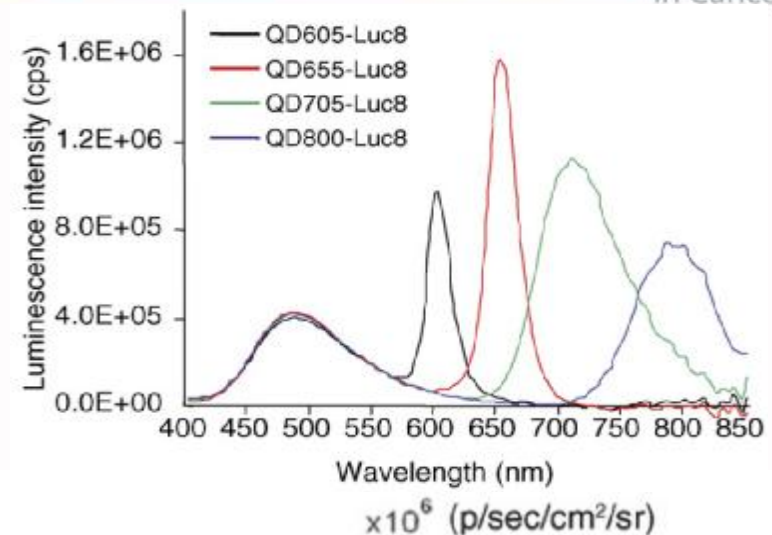
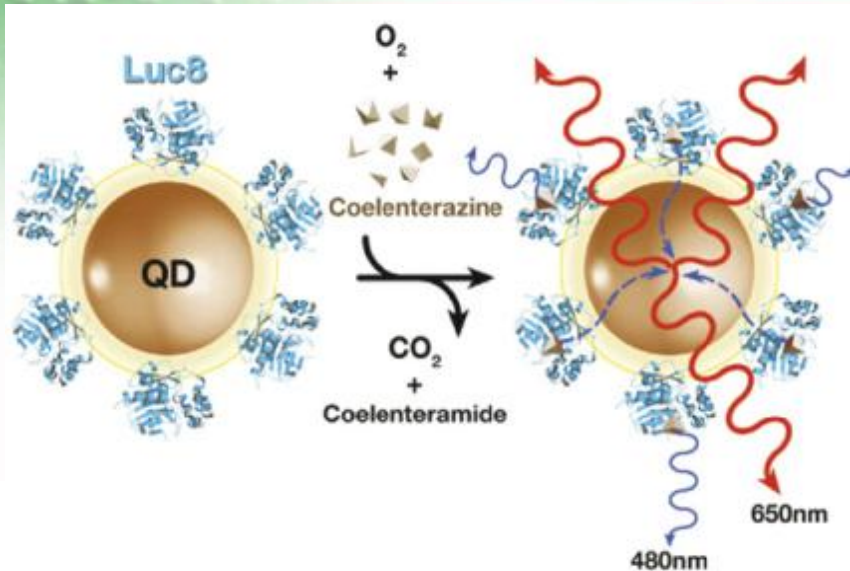
§ Detect target analytes through changes in nanowire's DC conductivity due to target binding to a surface-bound capture probe



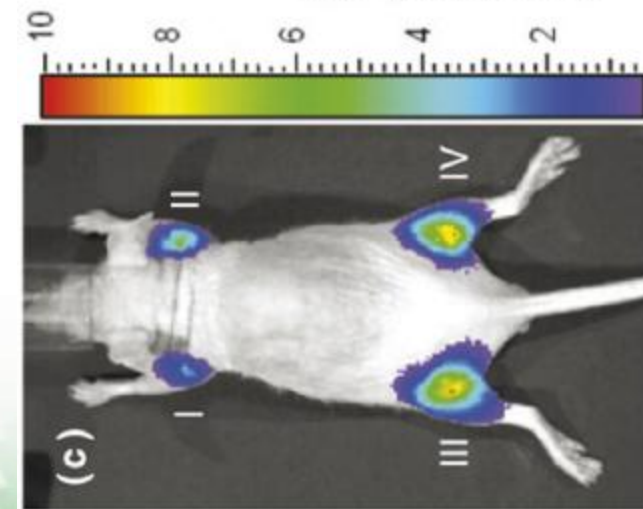
James Heath, Caltech

# Novel Quantum Dots That Do Not Require External Illumination

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- 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

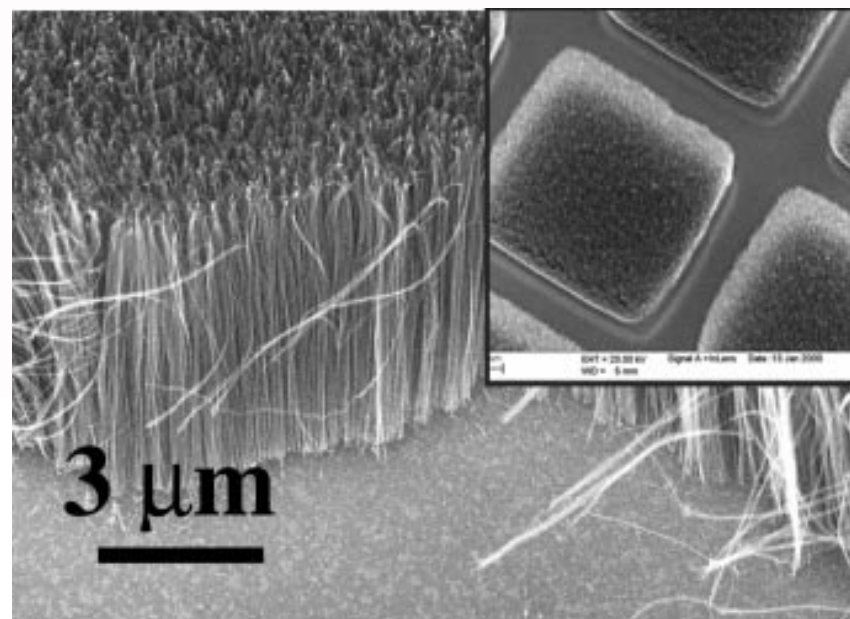




# Problem – Imaging Single Cells: X-rays From Carbon Nanotubes Irradiate Individual Cells

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- Exciting an individual carbon nanotube causes it to release high-energy electrons only from its tip, producing a high-energy electron beam with a diameter of 10 microns, small enough to irradiate specific locations in single cells.
- As many as 10,000 of these microbeam electrodes can be combined to produce an electron source capable of irradiating single cells or arrays of cells with a finely tuned dose of electrons.
- Radiation therapy is an important component of modern cancer therapy, but is a blunt weapon at best. Carbon nanotube-generated electron beams should give it scalpel-like precision.



S. Chang, et. al., *Radiation Protection Dosimetry*, 2007  
Image courtesy of O. Zhou, University of North Carolina at Chapel Hill

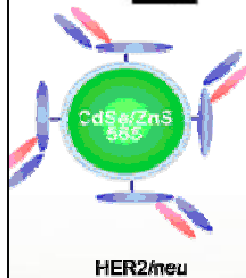
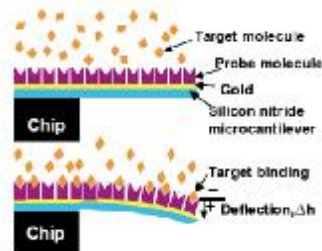
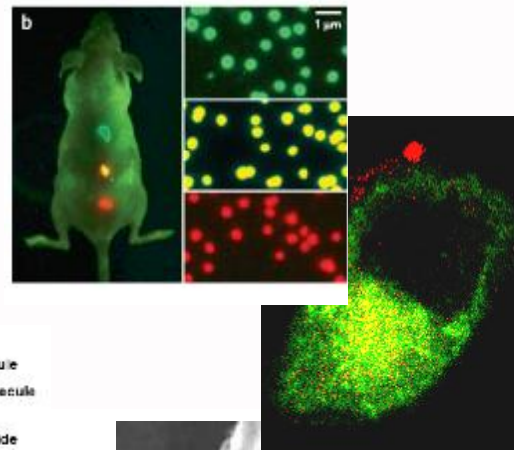
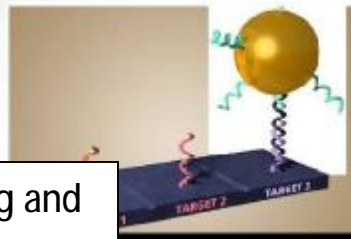


# Nanotechnology: Innovative Solutions for Complex Cancer Problems

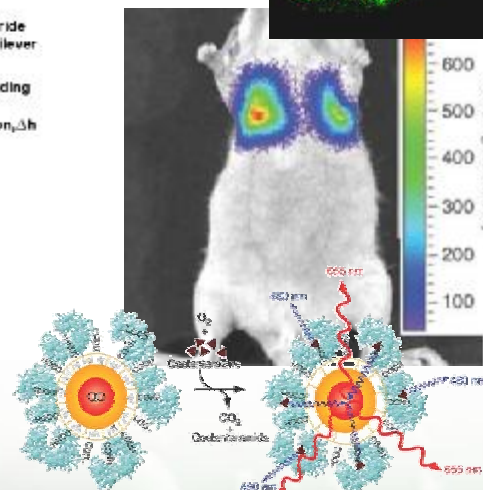
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## Focus Areas:

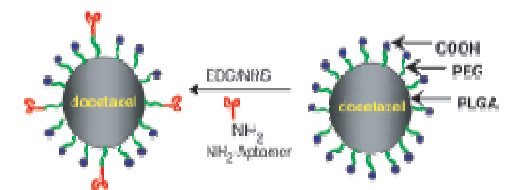
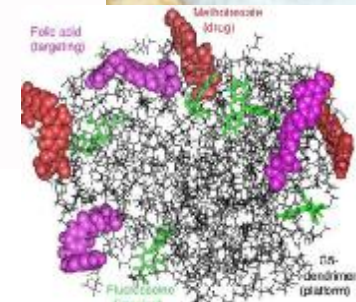
- Molecular imaging and early detection
- In vivo imaging
- Reporters of efficacy
- Multifunctional therapeutics
- Prevention and control
- Research enablers



Early detection



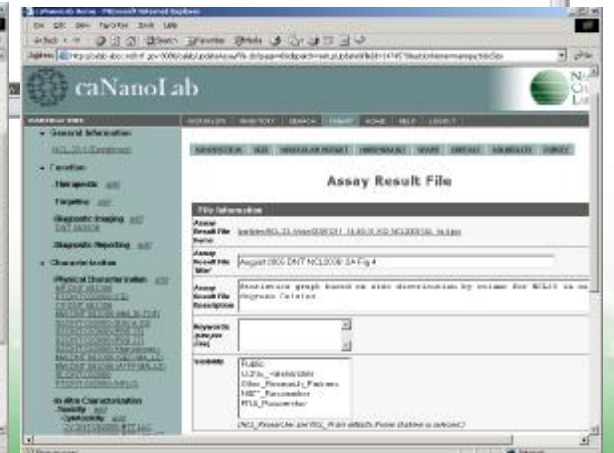
Imaging



Therapy

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- 
- The screenshot displays the caNanoLab web application running in a Microsoft Internet Explorer browser. The address bar shows the URL: <http://localhost:8080/caNanolab/naacrfnanoparticlesearch.do?search=setup>. The page features a red header with the National Cancer Institute logo and the text "National Cancer Institute" and "U.S. National Institutes of Health | www.cancer.gov". Below the header is a navigation bar with links: QUICK LINKS, WORKFLOW, HISTORY, SEARCH, ELIST, HOME, HELP, LOGIN. The main content area is titled "Search Nanoparticles" and contains a search criteria form. The form includes the following fields and options:
- Particle Source:** A dropdown menu.
  - Particle Type:** A dropdown menu set to "Diamond".
  - Function Type:** A list box containing "Therapeutic", "Diagnostic Imaging", and "Diagnostic Reporting".
  - Characterization Type:** A list box containing "Biological Characterization", "Physical Characterization", "Toxicity", "Cytotoxicity", "Immunotoxicity", "Biocompatibility", "Biodegradability", "Biocompatibility", and "Biocompatibility".
  - Keywords (per page):** A text input field.
  - Grid Node Name:** A list box containing "NCL", "which ngram University", and "Stanford University".
- On the right side of the search criteria form, there are radio buttons for "Nanoparticle" and "Acoustic Resonance".



# Nano-Challenges

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- Convergence of physical and biological (specifically molecular oncology) – broadening scope in an already complex field
- Education – engagement of oncologists
- Limitations of trained scientists and new training models
- Defining properties at the meso-scale
- Building from the ground up – understanding performance
- Sensors – communication from the nano to macro environments
- Clinical trials models
- Regulatory hurdles
- Public perception (nano-bots to invisibility) vs. real promise for medicine



# <http://nano.cancer.gov>

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**National Cancer Institute** U.S. National Institutes of Health | [www.cancer.gov](http://www.cancer.gov)

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Transforming the diagnosis, prevention, treatment and clinical outcomes for cancer patients

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**Nanotech Highlights**

[Request for Applications RFA-CA-06-010](#)  
Fellowships in Cancer Nanotechnology Research  
Receipt Date: November 16, 2005

[Nanotechnology in Cancer Spotlighted at NSTI Nanotech 2005](#)  
Speaker: Gregory Downing, D.O., Ph.D., National Cancer Institute

[NCI NCL Solicitation NOT-CA-05-011](#)  
Nanotech Strategies for Cancer Research

**DELIVERING**  
today's knowledge in  
Nanotech Oncology

**This Week's Nanotech News** [ view all ]

[Nanoscale "Cell Within A Cell" Delivers Multiple Therapies that Kill Tumors](#) Aug 1

[DNA Nanoparticles Deliver Genes Intravenously](#) Aug 1

[Nanostructured Scaffold Growing New Bladder Tissue](#) Aug 1

[Nanofluidics Produces Million-Fold Concentration of Proteins](#) Aug 1

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# A Noble Vision

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“A grand challenge is the ability to detect cancer earlier  
— ***and the answer almost certainly will be  
nanotechnology.***”

“In addition to detecting cancer, nano-based  
techniques will enable physicians to determine  
whether a particular treatment is working.”

***Dr. Richard Smalley, Nobel Laureate  
September 13, 2004***