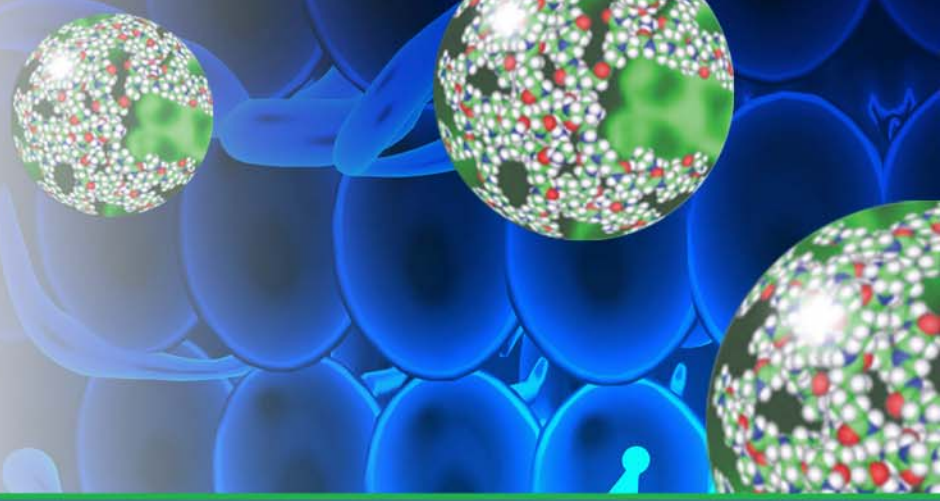
National Cancer Institute

NCI Alliance for Nanotechnology in Cancer



Cancer Nanotechnology – Opportunities and Challenges – View from the NCI Alliance for Nanotechnology in Cancer

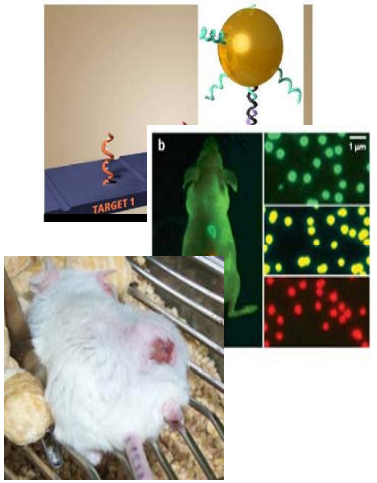
Updated January 21, 2011

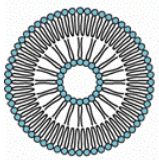
Piotr Grodzinski, Ph.D.
Office of Cancer Nanotechnology Research, NCI

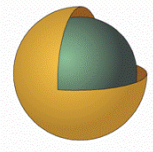
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

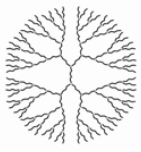
Cancer Nanotechnology: The Opportunity

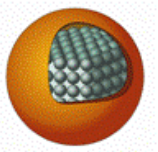
- Combine power of innovation in nano-materials and cancer biology to develop new solutions in cancer
- Detect disease *before* health has deteriorated
  - Sensors
  - Imaging
- Deliver therapeutics
  - Local delivery
  - Improved efficacy
  - Post-therapy monitoring
- Develop research tools to enhance understanding of the disease



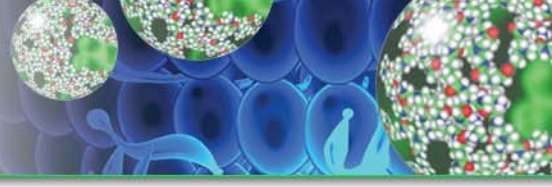

Liposome


Gold nanoshell


Dendrimer

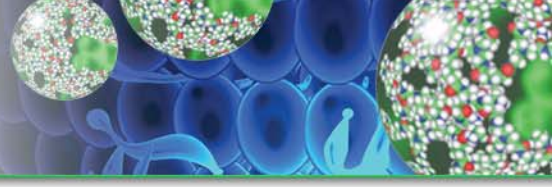

Quantum Dot

Why Nanotechnologies for Cancer?



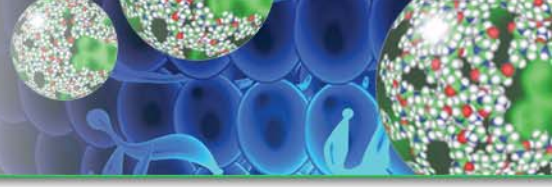
- Cancer can generally be successfully treated – if diagnosed early
- Cancer is exceedingly complex (potentially hundreds of genomic changes – possibly thousands of proteomic changes to measure for diagnosis) – power of multiplexed detection is needed
- Specific delivery of therapies to targeted cancer cells is critical – now and in the future
- Theranostic functions are necessary for diagnosing and treating cancer (need to detect – deliver – report – monitor – re-deliver)
- Probing and understanding changes in tissues/microenvironments are crucial to preventive strategies for cancer

Addressing Key Questions



- Enable understanding, prevention, detection, and elimination of metastases;
- Enable understanding and overcoming of multi-drug-resistance phenomenon (MDR);
- Monitor the tumor microenvironment, its heterogeneity, and its changes during tumorogenesis;
- Develop *in vivo* drug delivery techniques allowing for a significant increase in therapeutic index of highly potent, but toxic drugs;
- Develop nanoparticle-based siRNA delivery vehicles;
- Develop tools and devices which can penetrate cellular barriers that may limit devices accessibility to intended targets (notably including the blood-brain-barrier);
- Develop techniques allowing for capture, monitoring, and characterization of circulating tumor cells (CTCs);
- Develop methodologies for predictive modeling and understanding of nanomaterials' pharmacokinetics and pharmacodynamics in *in vivo* environment.

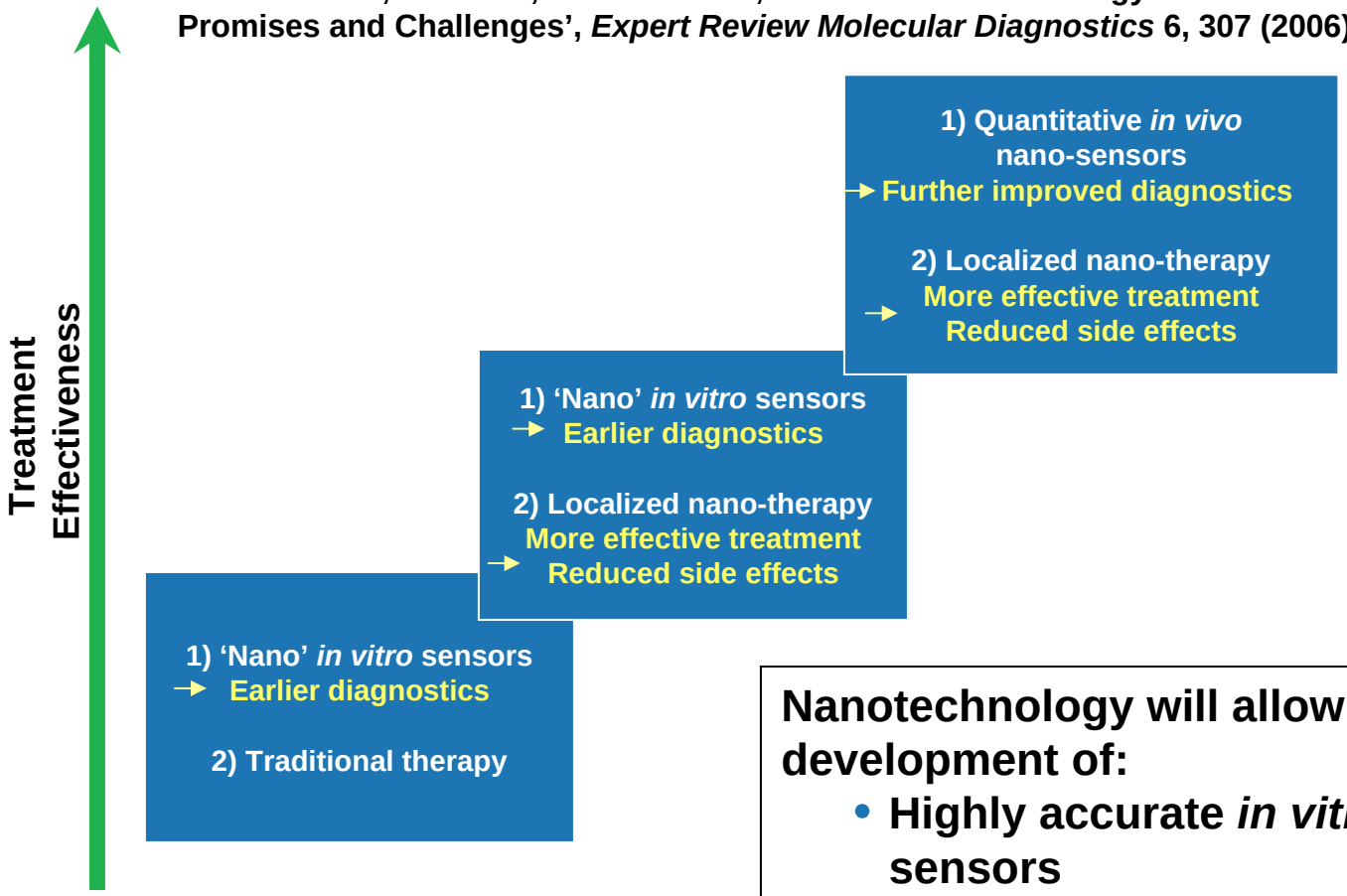
Nanomedicine 101



- **Let biology and oncology needs drive technology development**
  - Do not over-engineer – simple is beautiful!
- **Choose your targets and disease applications wisely**
  - Incremental improvement vs. solving an unsolved problem
- **Nanotechnology is a team sport – work with others**
- **Decide if you really want to be a translational researcher – it is hard**

Nanotechnology for Cancer: Evolution and Progress

P. Grodzinski, M. Silver, and L. Molnar, 'Cancer Nanotechnology – Promises and Challenges', *Expert Review Molecular Diagnostics* 6, 307 (2006)



Nanotechnology will allow for the development of:

- **Highly accurate *in vitro* and *in vivo* sensors**
- **Novel imaging contrast agents**
- **Platforms for localized therapy**

CSSI Strategy to Accomplish Goals of Contemporary Science

Engineering

Ωορκινγ τογετηερ

Biology

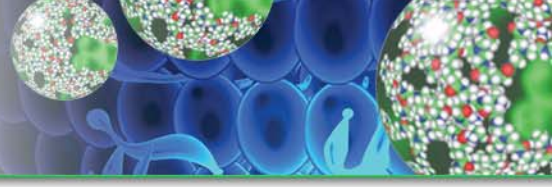
Medicine

Working together

Multi-disciplinary Team Research and Development is Necessity not an Option

- **Medical applications of nanotechnology require multi-disciplinary approach involving both technology developers and technology users in the process of innovation and product development**
- **Large research teams are proving to be more productive and innovative than single investigator efforts in the medical areas where technology involvement is necessary**

NCI Alliance for Nanotechnology in Cancer Achievement

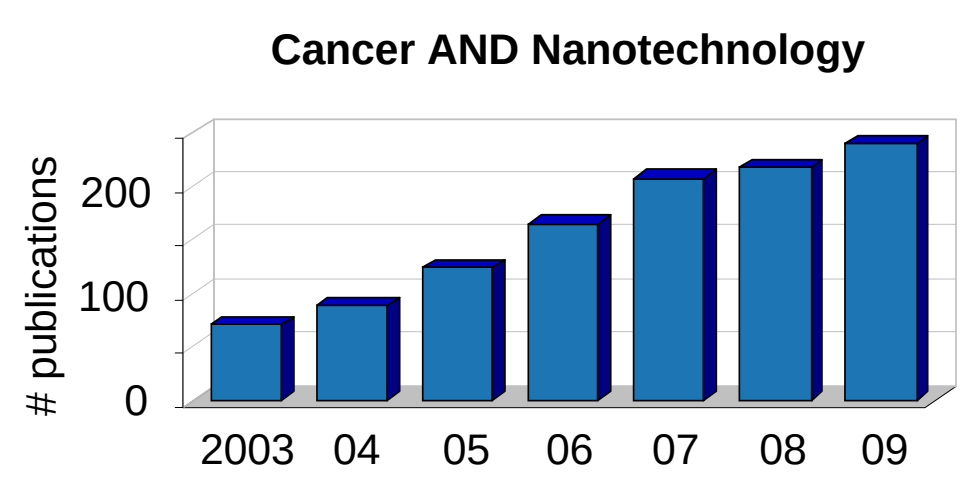


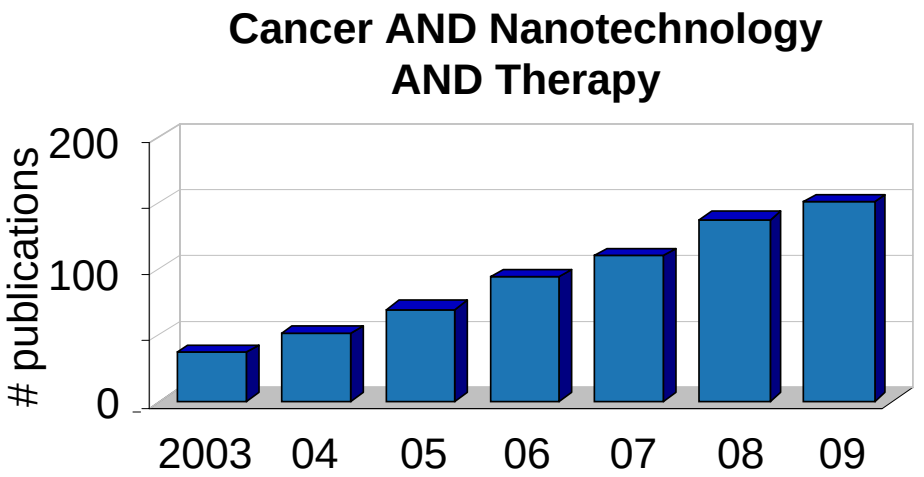
- **Centers of Cancer Nanotechnology Excellence (CCNE)**
- **Cancer Nanotechnology Platform Partnerships**
- **Multi-disciplinary Training Awards**
- **Nanotechnology Characterization Laboratory**

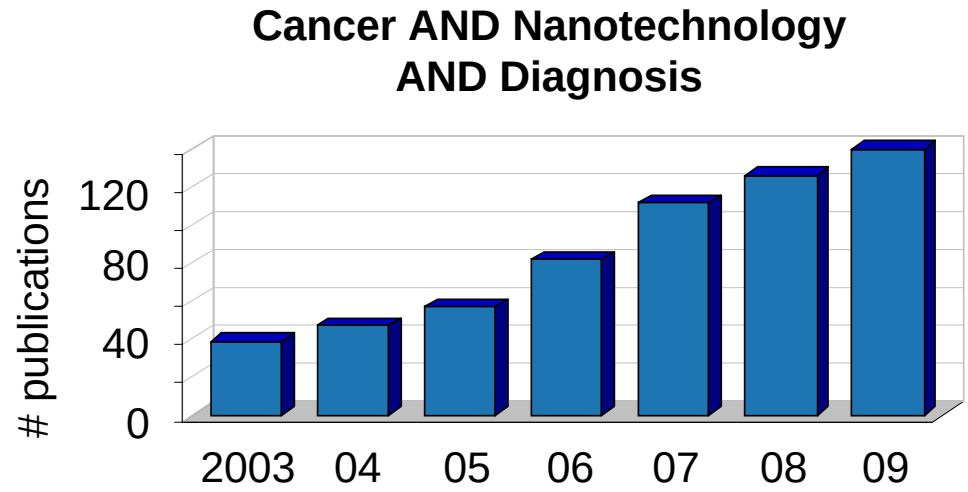
- **Scientific output** – over 1000 peer-reviewed journal papers published with average impact factor ~7
- **Clinical translation** – 50 companies associated with the program in the space of diagnostics and therapy; 34 were formed in last 4 years. Developing strong intellectual property portfolio – over 200 disclosures and patents filed
  - several clinical trials are associated with program projects
  - several companies are in pre-IND discussions with FDA
- **Leveraged funding** – investigators received numerous additional grants from peer-reviewed government sources, philanthropy, industry, and venture investors

Phase I: 2005 – 2010
Phase II: 2010 – 2015

Developing a Field of Cancer Nanotechnology







Cancer AND Nanotechnology AND Prevention : 40

Nanotechnology AND Metastasis: 45

Objectives for Phase II

The Alliance program was designed to develop research capabilities for multi-disciplinary team research, with the goal of advancing prevention, diagnostic, and/or treatment efforts.

Research Discovery

Pre-clinical

Clinical

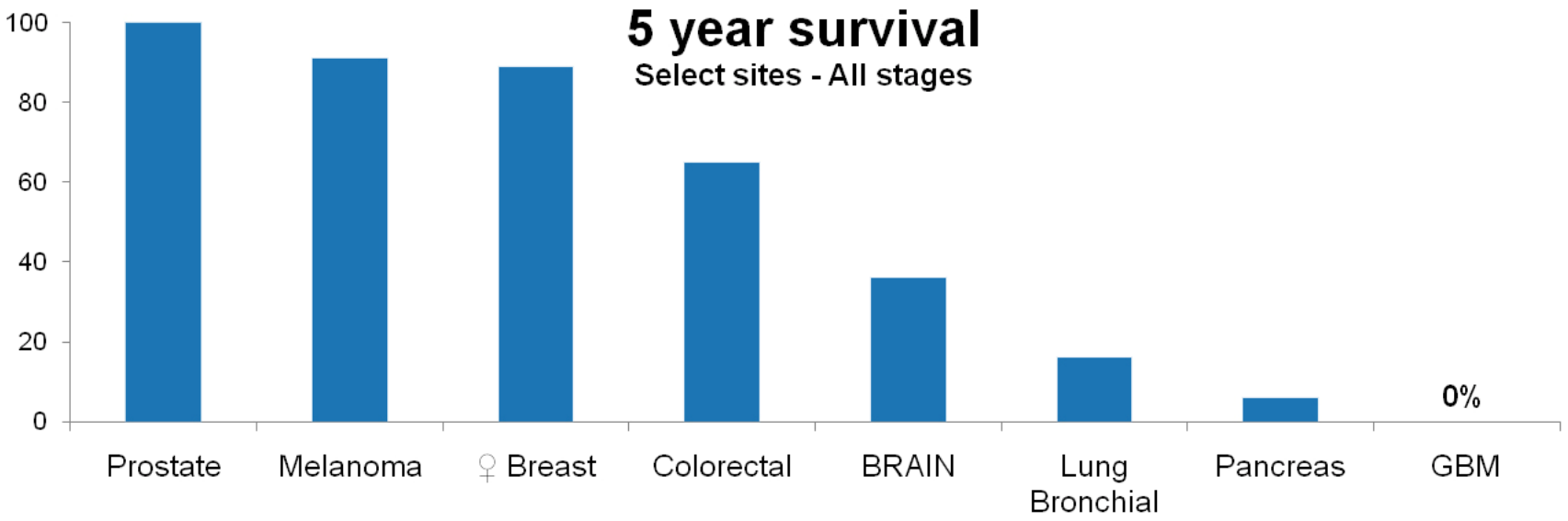
The Alliance's development model calls for the most promising strategies discovered and developed by ANC grantees to be handed off to for-profit partners for effective clinical translation and commercial development.

Challenge areas:

- Early diagnosis using *in vitro* assays and devices or *in vivo* imaging techniques
- Multifunctional nano-therapeutics and post-therapy monitoring tools
- Devices and techniques for cancer prevention and control

Focus on cancers with low survival rates such as brain, lung, pancreas, and ovarian cancer

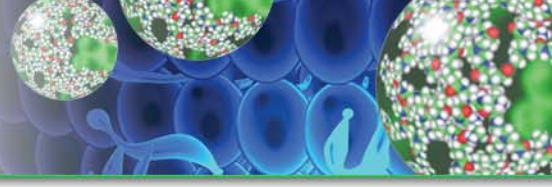
5 year Survival for Different Cancers

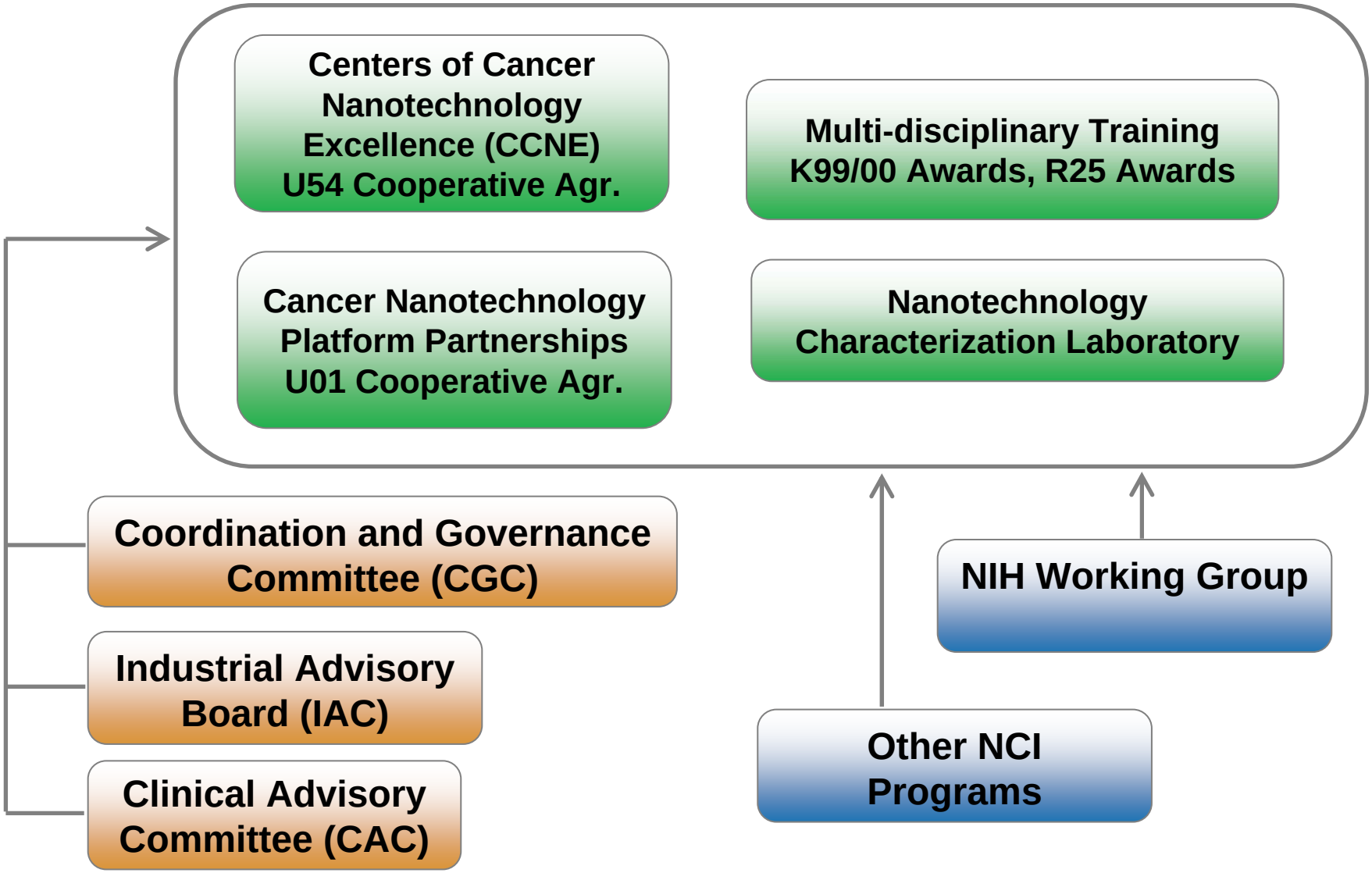


CA Cancer J Clin. 2010 Sep-Oct;60(5):277-300. Epub 2010 Jul 7

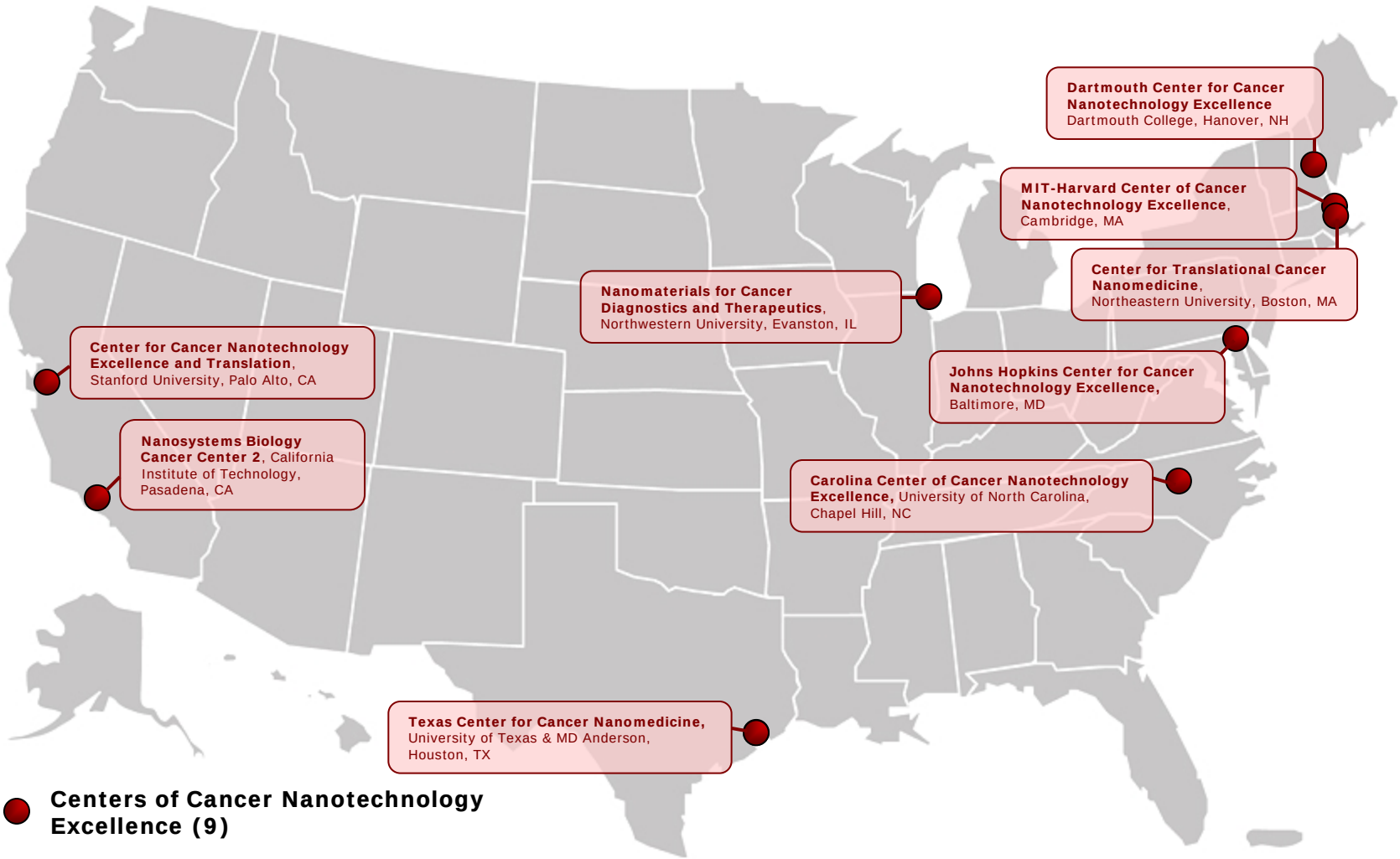
Focus program on cancers with low survival rates such as brain, lung, pancreas ,and ovarian cancer

NCI Alliance for Nanotechnology in Cancer Phase II - Organizational Structure

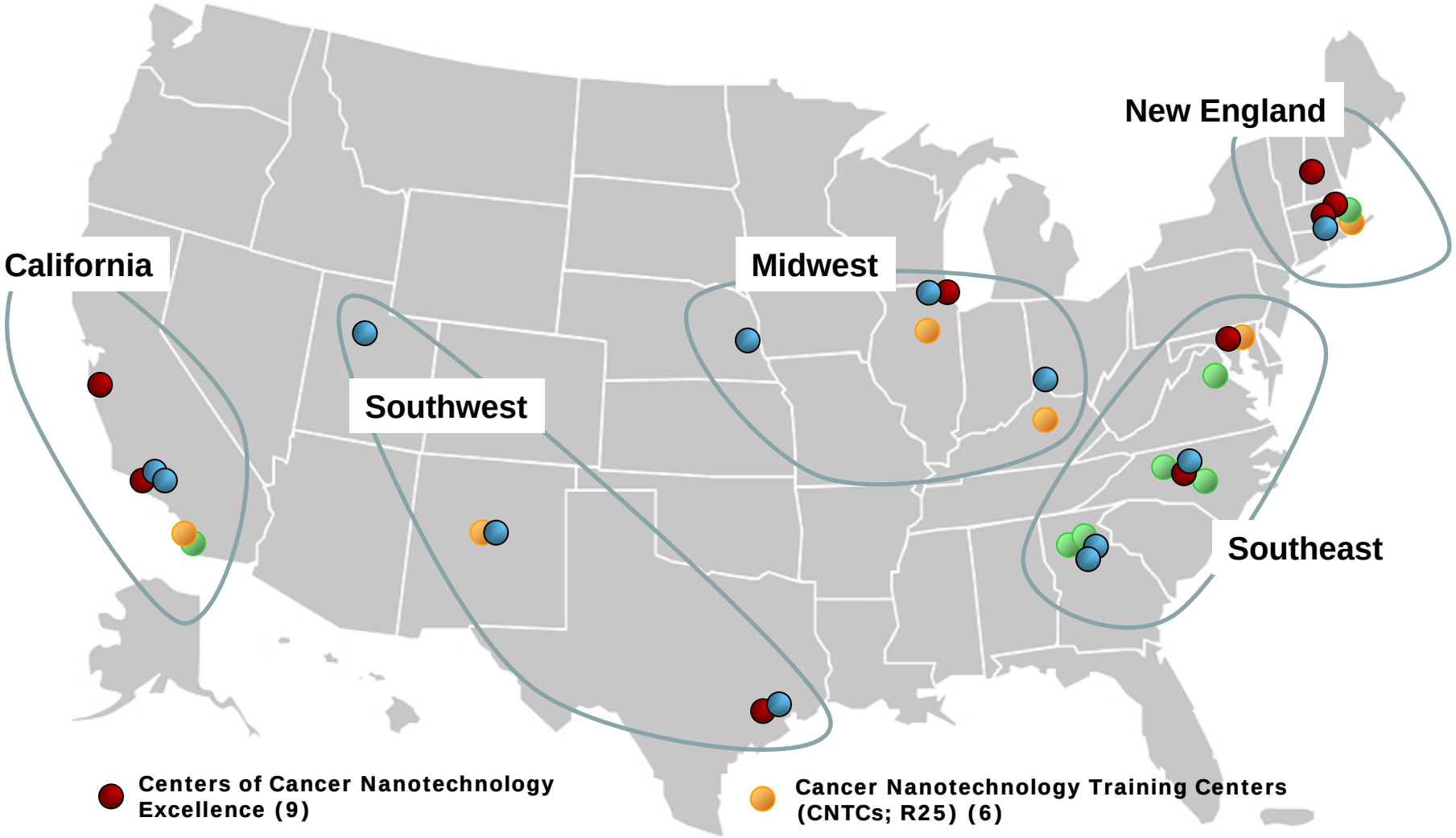




Centers of Cancer Nanotechnology Excellence (U54)



NCI Nanotechnology Alliance Awardees 2010



Education/Training and Outreach Programs

- Centers of Cancer Nanotechnology Excellence
- Cancer Nanotechnology Training Centers
- K99/R00 Awards
  - Integrative training for multi-disciplinary researchers
  - Physical science approaches applied to cancer research
  - Graduate programs, fellowships, certifications, courses

In vitro Diagnostics

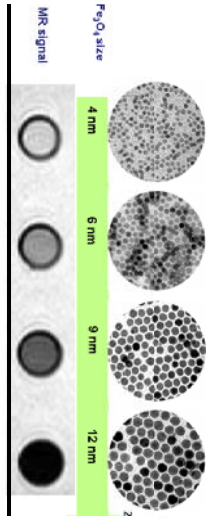
Organ Site	Test
Bladder	None
Breast	Mammogram
Cervix	Pap smear
Colorectal	Fecal occult blood test, sigmoidoscopy, colonoscopy, double contrast barium enema, digital rectal exam
Esophageal	None
Kidney	None
Liver (primary)	None, but two molecular tests are approved for risk assessment
Lung	Imaging
Ovary	None proven to decrease mortality
Pancreatic	None
Prostate	None proven to decrease mortality

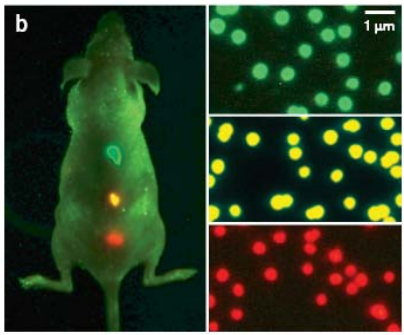
Early detection tests
EDRN report, 08

- Biomarker discovery
- Development of modular diagnostics based on bodily fluids, such as blood, serum, cerebrospinal, urine, stools, or saliva
- Techniques to monitor and capture circulating tumor cells from blood
- Multifunctional capabilities – one platform capable of detecting nucleic acid and protein

Imaging and Nanotechnology

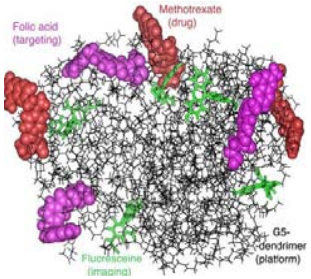
- Develop minimal or non-invasive methods allowing access to organs such as brain, pancreas, lungs, and ovaries and to help better understand *in vivo* tumor biology
- Improve spatial and temporal resolution, as well as sensitivity, in order to detect the very low tumor burdens, improve surgical guidance, and monitor the response of those small tumors to therapy
- Develop image-guided biopsies with simultaneous, multiplexed *in situ* analysis to eliminate the need for diagnoses based on histopathology
- Develop intra-operative techniques to monitor margins of removed issue in real time
- Use nanotechnology elements to develop more sensitive and less expensive imaging hardware – carbon nanotube-based CT instruments





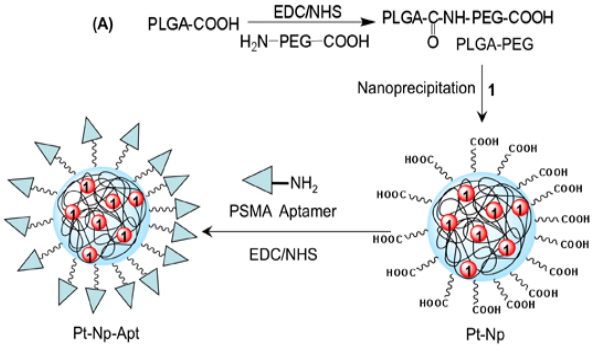
Nano-therapy Strategies

Delivery of chemotherapeutics



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

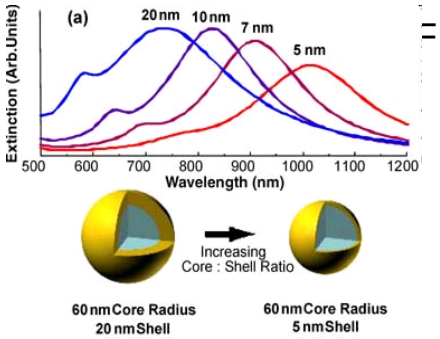
Pro-drug strategy



Dhar, Langer et al. PNAS (2008) 105: 17356

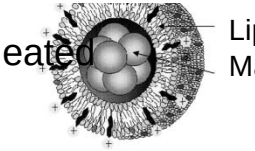
Hyperthermia

Photothermal

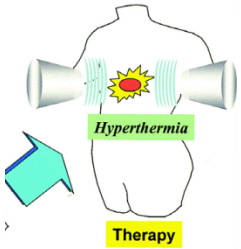


N. Halas, J. West et al, Ann Biomed Eng. (2006) 34: 15

= heated

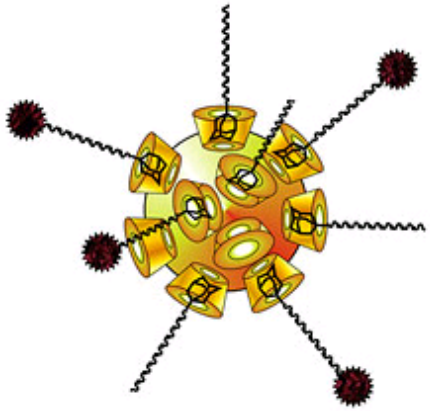


Liposome
Magnetite nanoparticle



A. Ito et al., J. of Bioscience and Bioeng. (2005 100: 1)

Genetic therapy

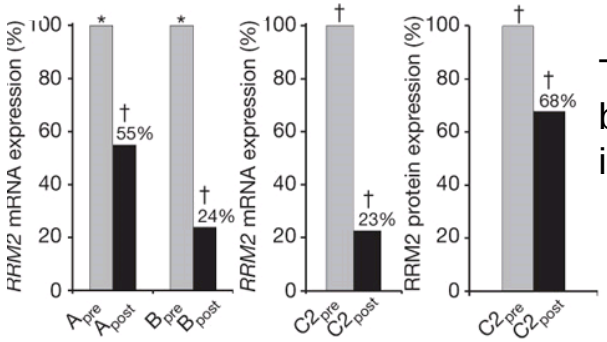


M. Davis et al. Nature (2010) 464: 1067

First Targeted Delivery of siRNA Using Cyclodextrin Polymer-Based Nanoparticles

- Free siRNAs do not produce efficient and predictable therapeutic effects:
  - siRNA deterioration in contact with blood
  - Majority of siRNA is removed from circulation by hepatic and renal clearance – only very small percentage reaches cells
  - The efficiency of siRNA passively entering target cells is very low

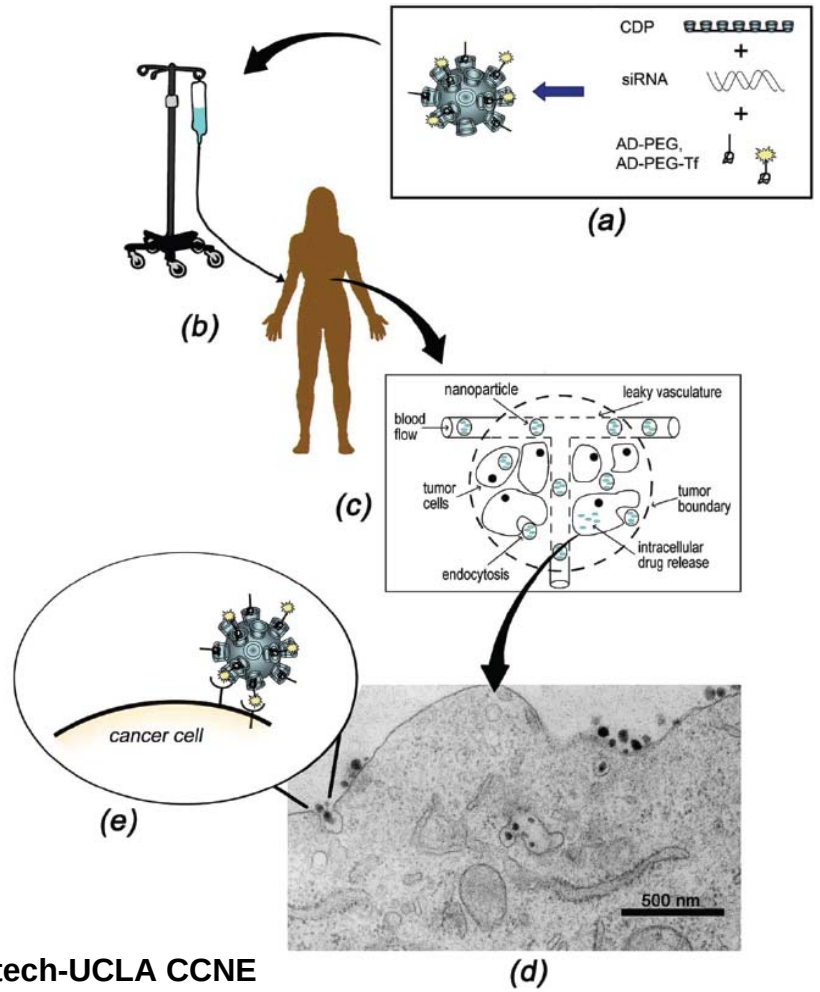
Deliver siRNA to reduce expression of RRM2



Tissue analysis before and after injection

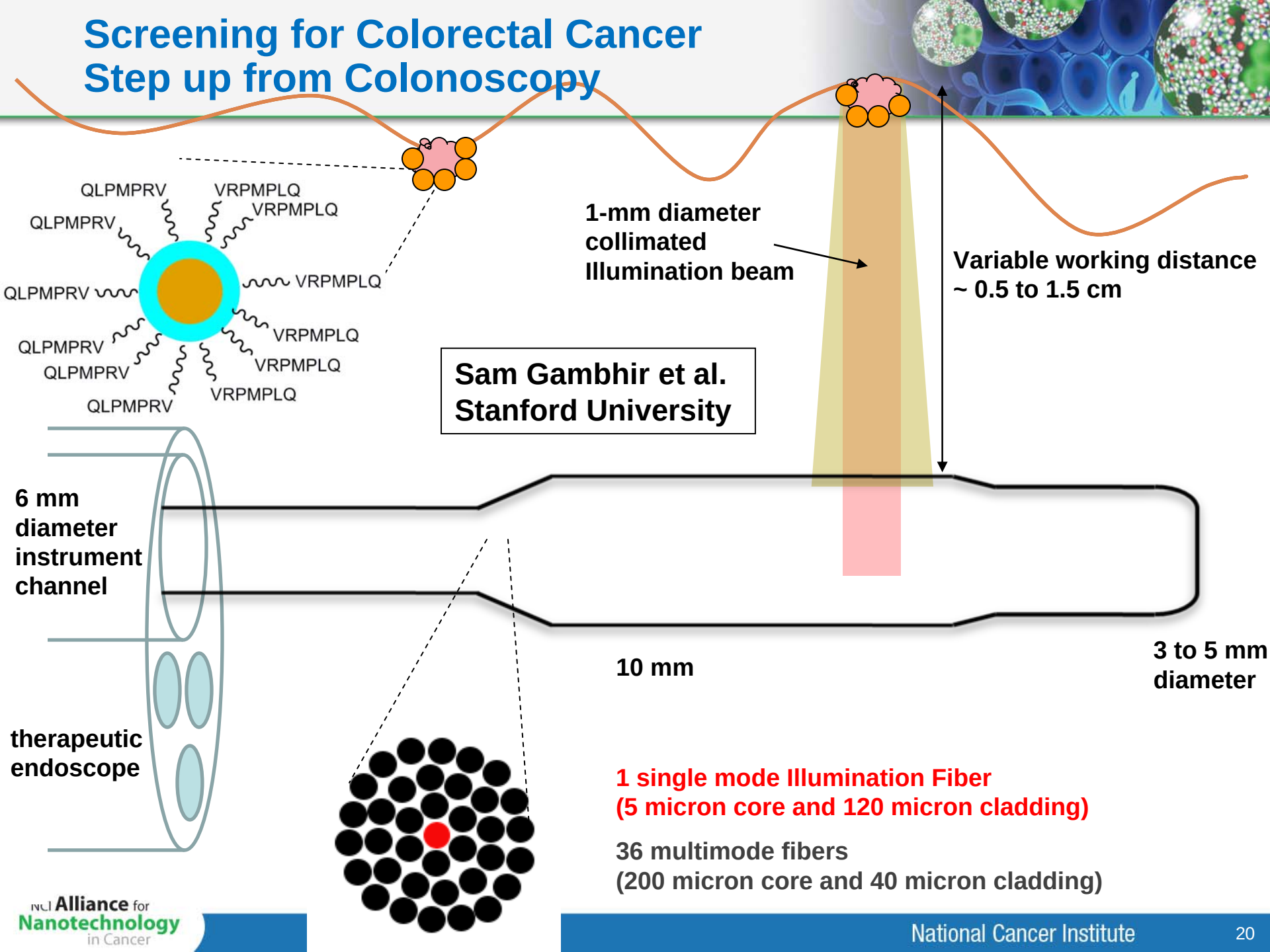
- RRM2 mRNA reduction
- RRM2 protein reduction

Cyclodextrin-based siRNA delivery

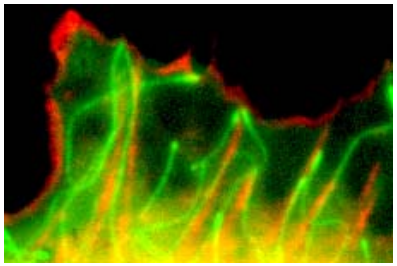


M. Davis – Caltech-UCLA CCNE
Nature (2010) 464: 1067

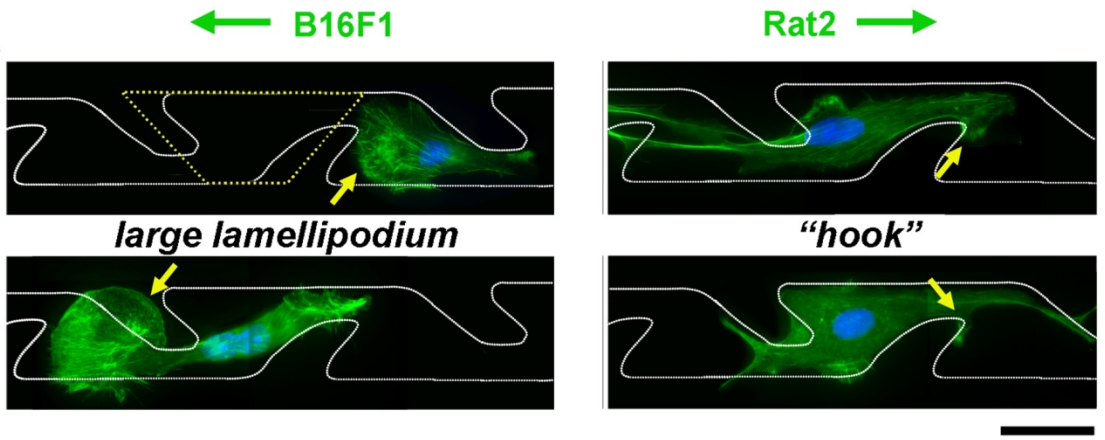
Screening for Colorectal Cancer
Step up from Colonoscopy



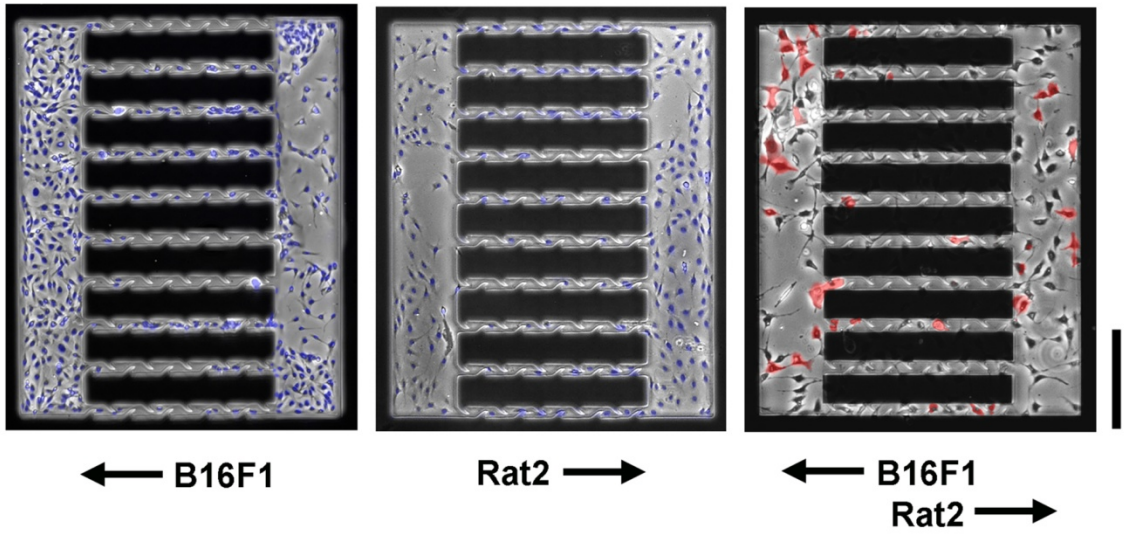
Geometric Sorting of Cancer Cells



- Microtubules ~ 25 nm
- **Focal Adhesions ~ 500 nm**

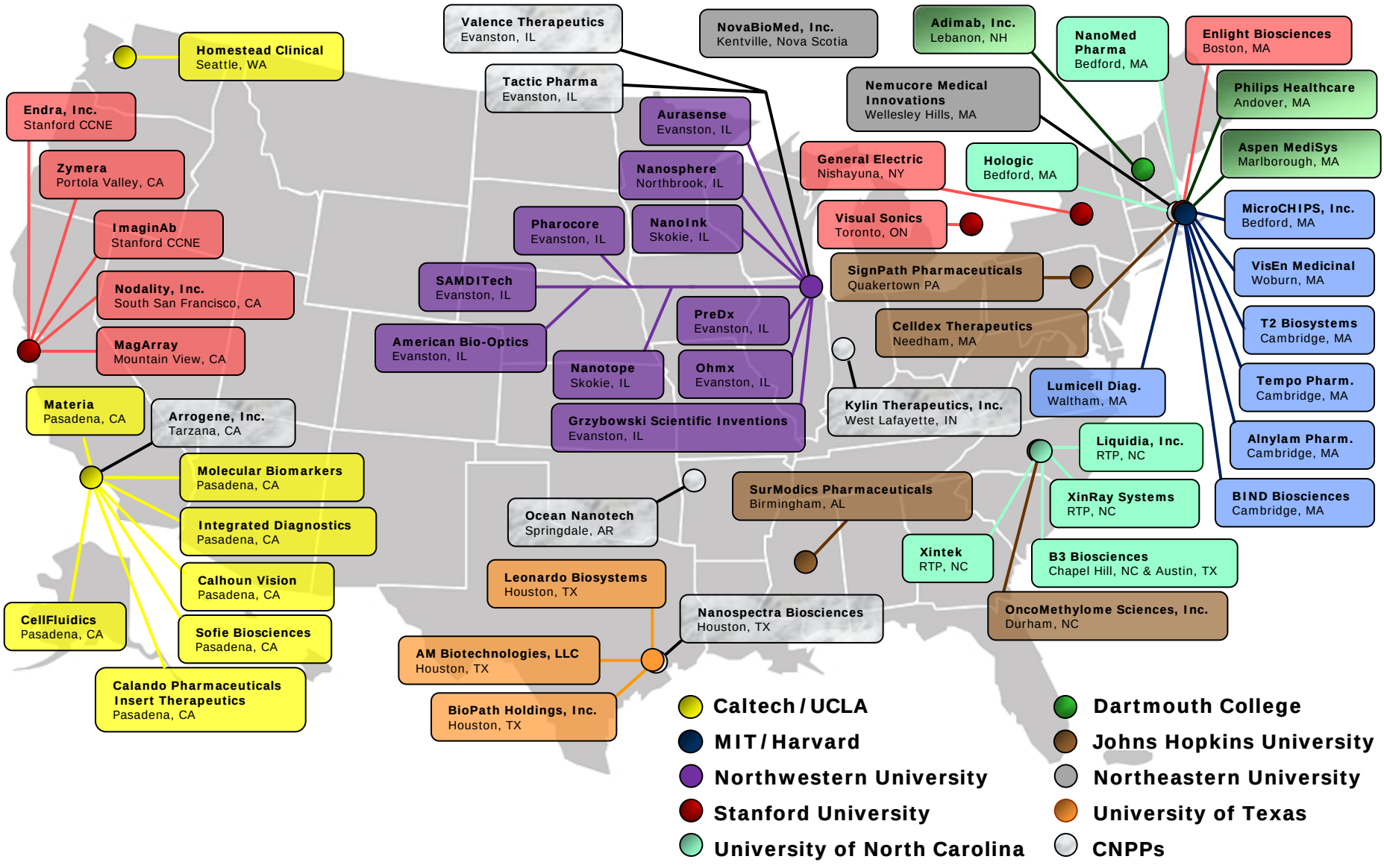


- To **control** organization of the cell motility machinery
- To **understand** their functions in **normal vs. cancerous** cells and identify molecular targets for anti-cancer therapeutics
- To **develop** robust screening procedures and identify drug candidates targets

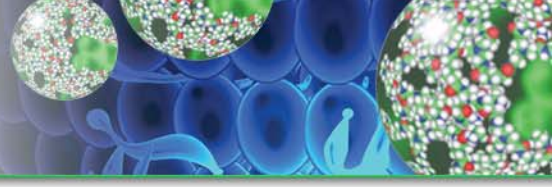


B. Grzybowski - Northwestern CCNE
Nat Physics (2009) 5: 606

NCI Alliance for Nanotechnology Commercial Partners

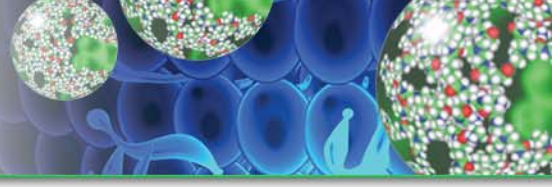


Alliance Investigators and Clinical Trials



- ***In vitro* assays:**
  - Testing of PSA clinical samples using bio-barcode – Mirkin, Thaxton, Northwestern U.
  - Blood Barcode Microfluidics – Heath, Mischel - Caltech/UCLA
  - Glioblastoma tissue analysis – Heath, Mischel - Caltech/UCLA
- **Imaging:**
  - PET agent synthesized in microfluidics – Phelps, Radu, Czernin - UCLA
  - MRI agent – Kereos and Lanza, Wickline, Wash. U.
  - MRI agent – Weissleder, Harvard
- **Therapy**
  - Adenovirus nanoparticles for immune gene therapy - Kipps, UCSD
  - Immunotherapy for melanoma – Heath, Witte, Ribas, Radu – Caltech/UCLA
  - Camptothecin on polymeric nanoparticles - Cerulean and Davis – Caltech
  - Docetaxel on polymeric nanoparticles – BIND and Langer/Farokhzad – MIT/Harvard
  - siRNA on polymeric nanoparticles - Calando Pharm. and Davis, Ribas, Czernin - Caltech
  - siRNA – Alnylam and Sharp - MIT

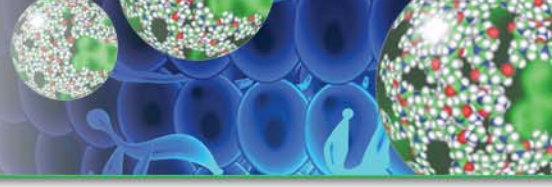
Nanotherapeutics Approved for Oncological Applications



- **Abraxane®** (albumin-bound paclitaxel, Abraxis BioSciences). FDA approval in 2005 for metastatic breast cancer
- Liposomal:
  - **Doxil®** (liposomal-PEG doxorubicin; Ortho Biotech/ Schering-Plough). FDA approval in 1995 for HIV-related Kaposi's sarcoma, metastatic breast cancer, metastatic ovarian cancer
  - **DaunoXome®** (liposomal daunorubicin; Gilead Sciences/ Diatos). FDA approval in 1996 for HIV-related Kaposi's sarcoma
  - **Myocet®** (liposomal doxorubicin; Zeneus). FDA approval is pending for metastatic breast cancer
- Polymeric:
  - **Genexol-PM®** (Methoxy-PEG-poly(D,L-lactide) taxol; Samyang, Korea). Approved in S. Korea for metastatic breast cancer. Phase II for pancreatic cancer in the US
  - **Oncaspar®** (PEG–L-asparaginase; Enzon). FDA approval in 2006 for Acute Lymphoblastic Leukemia

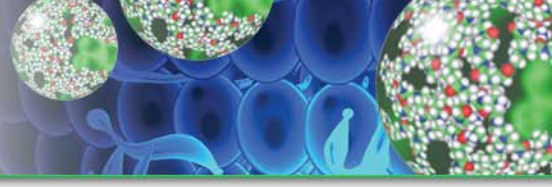
Several companies are close to filing IND applications with FDA for nanotechnology products

Pre-clinical Stage



Company	Product(s)	Material	Application	Status	Admin.
Avidimer	Platform, ATI-001	Targeted dendrimer	Imaging, therapy	Pre-clinical	IV
BIND	Platform technology	Targeted polymer nanoparticle	Therapy	Starting Phase I	IV
Liquidia Technologies	Platform technology	PRINT™ nanoparticles	Imaging, therapy	Pre-clinical	IV
Aurasense	Nano-flare	Gold	In-vitro diagnostics	Pre-clinical	
MagArray	GMR bio-sensor	Semiconductor device	In-vitro diagnostics	Pre-clinical	
Xintek	CNT-based X-ray	Carbon nanotubes	Imaging	Pre-clinical	

Regulatory Landscape

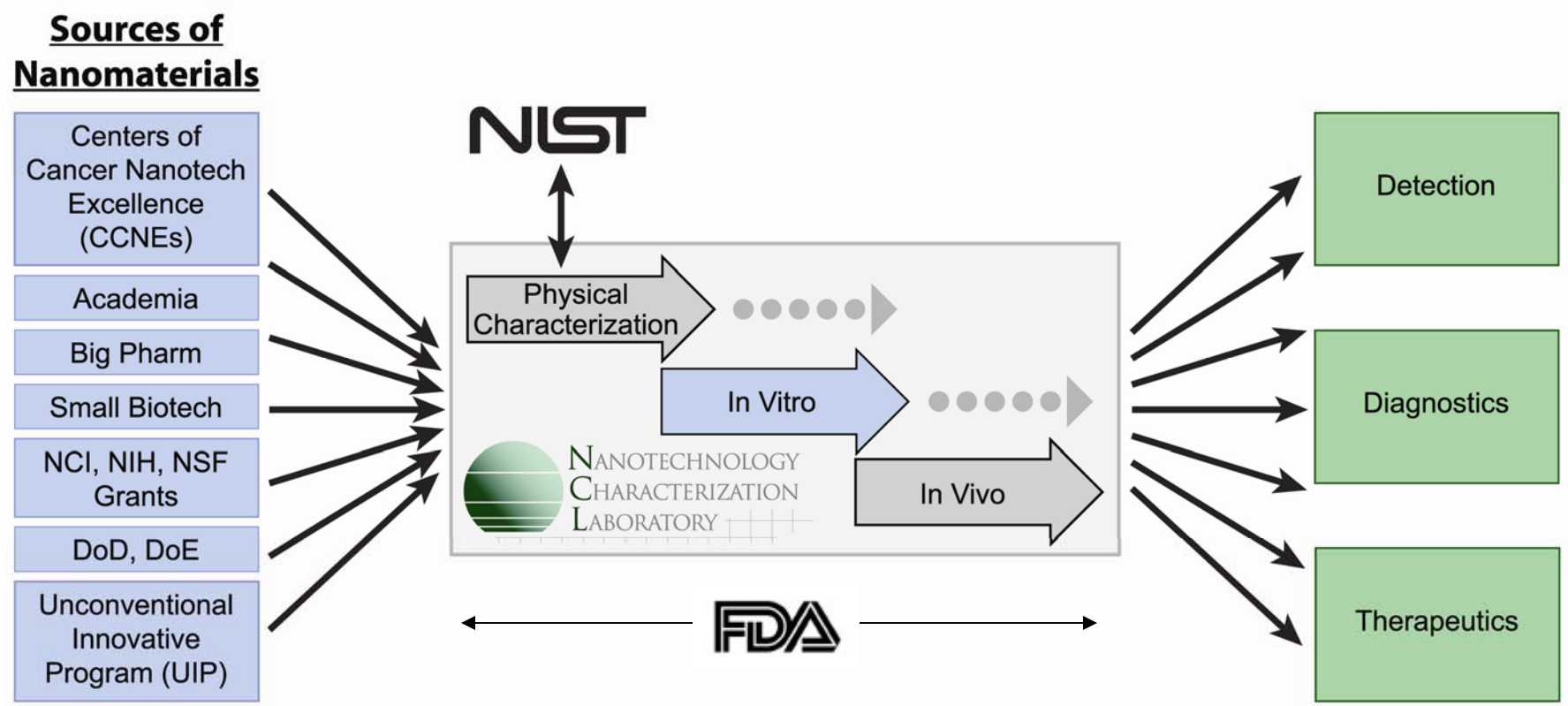


- Differences between the development and regulatory pathway for **multi-functional** nanoparticles and “traditional” drugs and devices
- Determination if the delivery construct should be qualified as ‘device’ or as ‘drug’
- Funding gaps between technology development in an academic setting and further technology maturation through clinical development and regulatory approval

Despite these challenges, FDA is now well positioned to evaluate nanotechnology-based formulations.

Nanotechnology Characterization Laboratory: Serving the Community

Scott McNeil



NCL is a formal collaboration between NCI, FDA ,and NIST

Nanotechnology Characterization Laboratory: Serving the Community

- *In vivo* Studies:
  - - 24 efficacy/tox/PK studies per year
  - MRI, PET and other *in vivo* imaging with SAIP
  - Non-human primate studies with NCTR
  - Efficacy studies on Transgenic mouse models with CAPR

LASP
Laboratory Animal Sciences Program

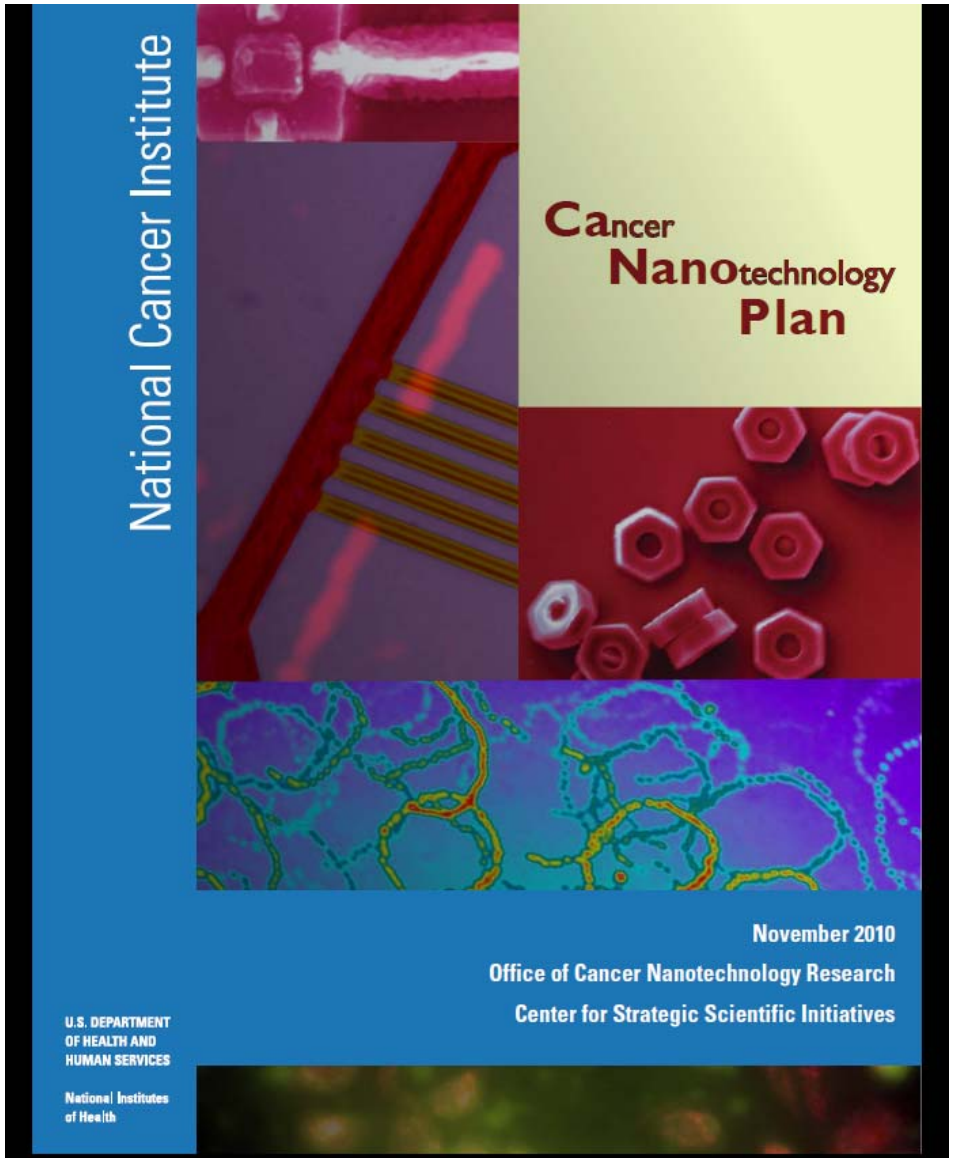
- Collaborations within NIH, FDA, NIST, NIEHS
  - NTP, EPA and others.
- Standards development efforts in collaboration with NIST, ASTM, ISO, IANH
- Inter-laboratory Studies
- caNanoLab co-development

Common Data Storage: caNanoLab Database

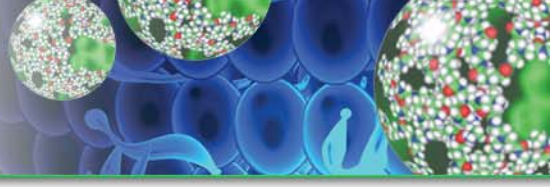
- Polydispersity and lack of standardized protocols
- Capture and exchange of information on composition and synthesis of nanomaterials, physico-chemical, *in vitro*, and *in vivo* characterizations as well as protocols
  - 28 protocols for nanoparticle characterization assays
  - 650 nanoparticle formulations
  - 2411 characterization
    - 787 physico-chemical
    - 1538 *in vitro*
  - More than 1100 publications

https://wiki.nci.nih.gov/display/ICR/caNanoLab

Forward Strategies

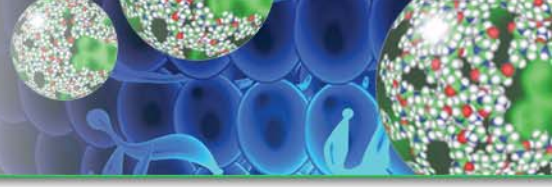


High Impact Cancer Nanotechnology Goals



- Early diagnosis of cancer in pre-metastatic stage:
  - point-of-care nano-devices for broad medical applications including cancer using unprocessed bodily fluids, with multiplex capabilities and rapid analysis
  - diagnostic and post-therapy monitoring nano-devices for interrogation of circulating tumor cells
- Successful delivery of therapies based on siRNA and other difficult to deliver molecules
- Novel nanoparticle-based chemotherapeutic formulations with lower toxicity and higher efficacy
- Theranostic constructs for diagnosis and subsequent localized therapy
- Effective diagnosis and delivery of therapies to brain, ovary, and pancreas

Current Status and Future Strategy



- Devices to diagnose the disease
- Devices to treat the disease
- Devices to monitor the disease in post-treatment stage

Translate and develop….

- Tools and devices to understand the processes behind the development and spread of the disease
- Devices to reverse/alter the progress of the disease

Acknowledgements
Office of Cancer Nanotechnology Research

Dorothy Farrell

Nicholas Panaro

Krzysztof Ptak

Sara Hook

Consultants:
Subhas Malghan – FDA
Duane Mitchell – Duke
Uma Prabhakar – formerly J&J

George Hinkal