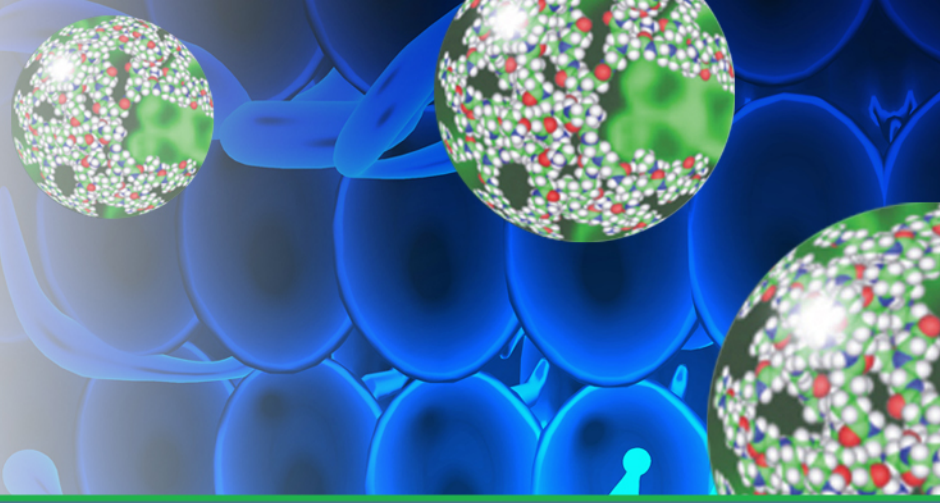
National Cancer Institute

NCI Alliance for Nanotechnology in Cancer



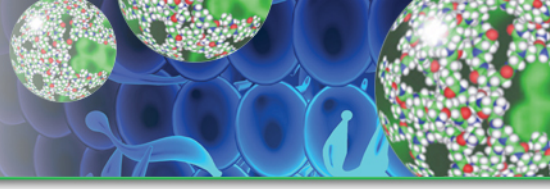
Cancer Nanotechnology – Opportunity for Novel Therapeutics and Diagnostics

September 12, 2012
NFAC meeting

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

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

NCI Alliance for Nanotechnology in Cancer Phase II (start in 2010)



Centers for Cancer Nanotechnology Excellence (CCNE) U54 Cooperative Agr.

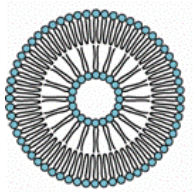
Cancer Nanotechnology Platform Partnerships U01 Cooperative Agr.

Multi-disciplinary Training Awards: K99/R00 and R25

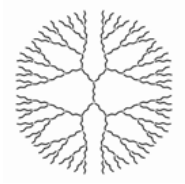
Nanotechnology Characterization Laboratory

- **Scientific output** – over 500 peer-reviewed journal papers and close to 100 patents and patent submissions published
- **Clinical translation** – over 70 companies in the space of diagnostics and therapy are associated with the program. Majority of them are start-ups.
  - 16 clinical trials are associated with program projects
  - several companies are in pre-IND discussions with FDA
  - formed a consortium to involve large pharma and biotech companies to assist translational process
- **Provocative Questions RFA** – disproportionately large number of awards made to nanotechnology based proposals – total of 7: 6 R01s and 1 R21

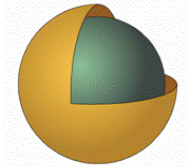
Different Particles and Different Methods of Making Them



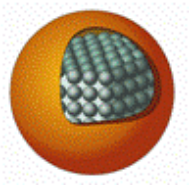
Liposome



Dendrimer

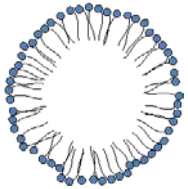


Gold nanoshell



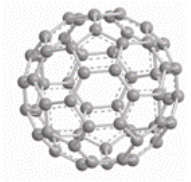
Quantum Dot

Colloidal gold

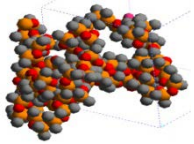


Nanoemulsion

Carbon nanotube



Fullerene



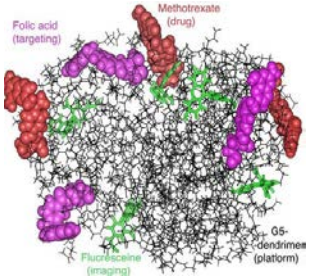
Polymers

Why we formed NCL? - need for a comprehensive assay kit to evaluate different nanomaterials

- Covalent organic synthesis
  - Dendrimers, Polymers
- Self-assembly
  - Liposomes, Emulsions, Micelles
- Crystal formation
  - Metal nanoparticles, Quantum dots
- Laser ablation, CVD
  - Fullerenes, carbon nanotubes
- Grinding/milling/fabrication
  - Organic and Inorganic Crystals

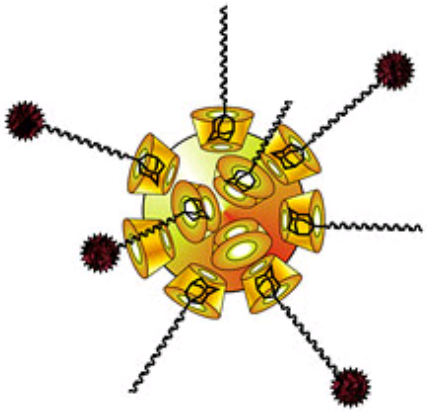
Nano-therapy Strategies

Delivery of chemotherapeutics



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

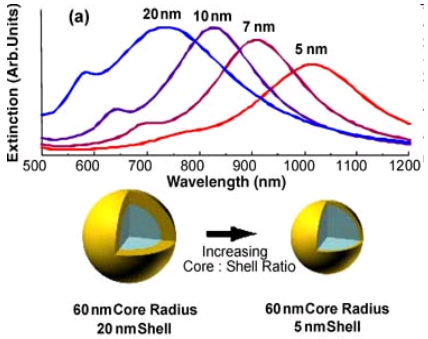
Delivery of siRNA



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

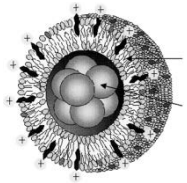
Hyperthermia

Photothermal



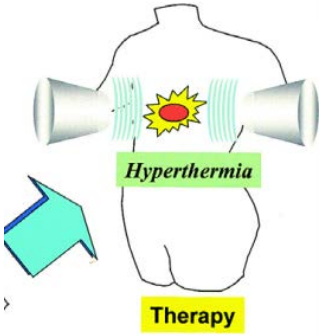
N. Halas, J. West et al, Ann Biomed Eng. (2006) 34: 15

RF-heated



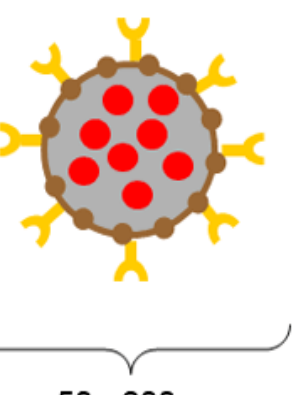
Liposome
Magnetite nanoparticle

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



Docetaxel-Encapsulated PLGA Nanoparticle-Aptamer Conjugates

Polymeric platform for drugs or biologics delivery



Targeting ligand → aptamers (nonimmunogenic, stable in a wide pH range & temperature)

Surface functionalization → PEG (increased stability)

Polymer matrix → PLGA (controlled released polymer)

Therapeutic payload → small molecules, peptides or nucleic acids

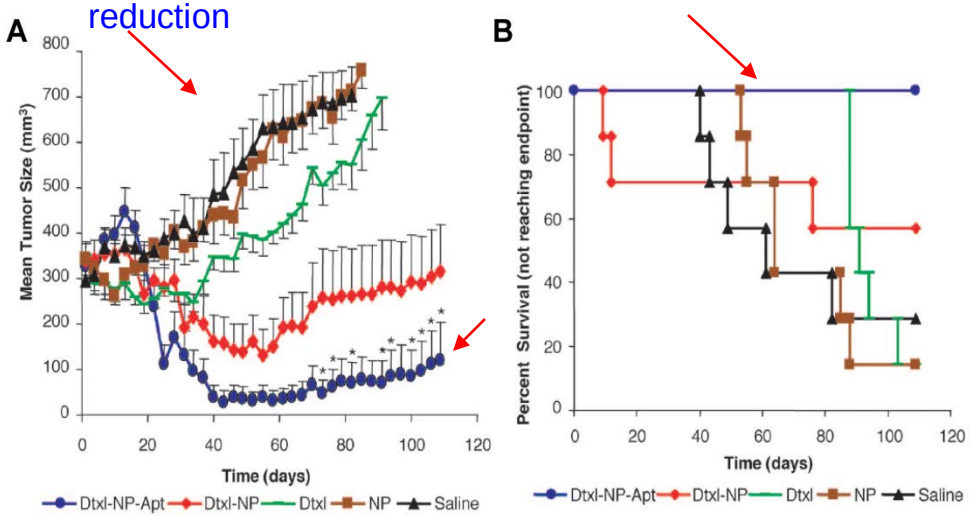
Advantage: increased efficacy & reduced toxicity

Approach:

- Docetaxel delivery to prostate cancer
- Aptamer recognizing PSMA on prostate cancer cells (LNCaP cell line)
- The comparative efficacy study of intratumoral injection (40 mg/kg) was evaluated over 109 days

Targeted NPs are more effective in tumor size reduction

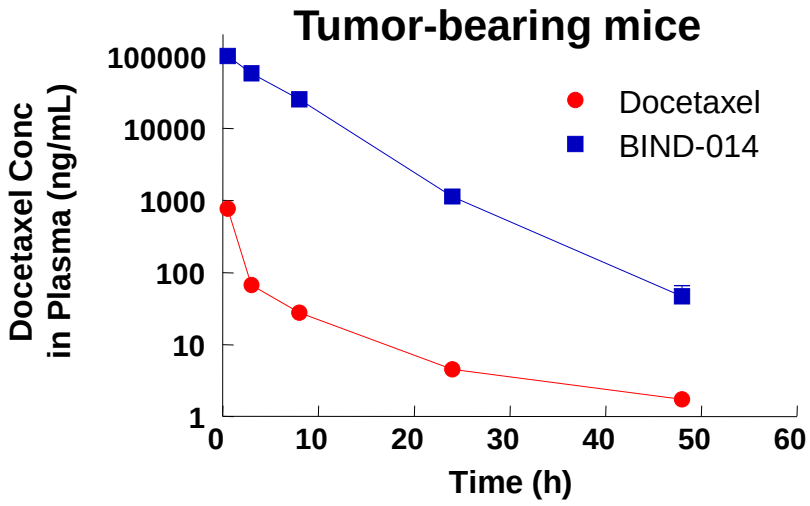
100% of the targeted NPs group was alive on day 109

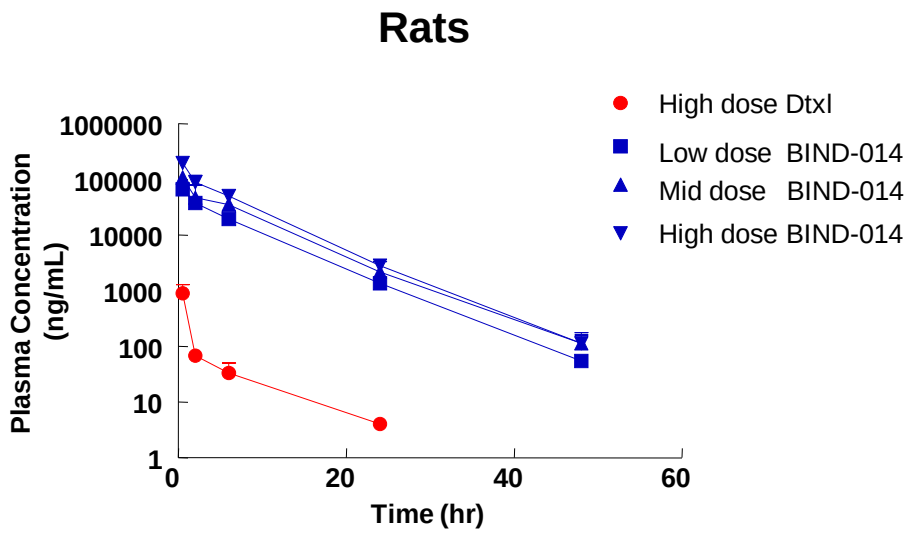


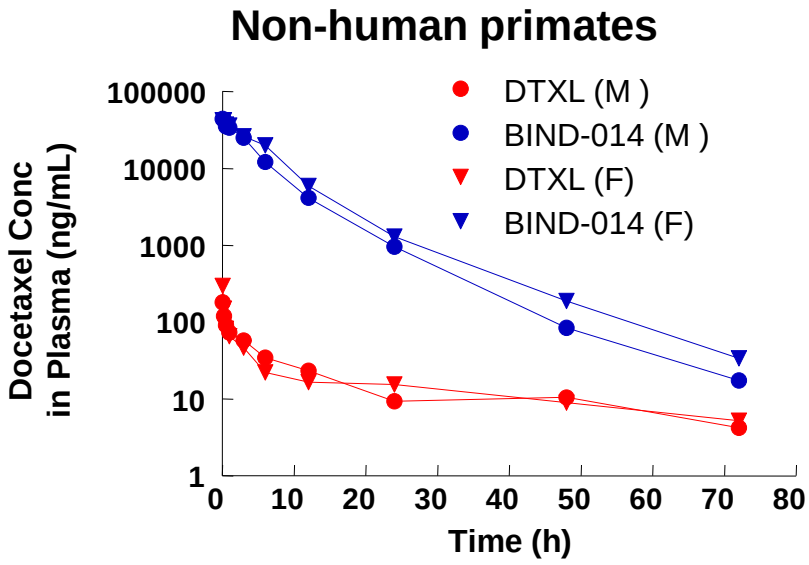
Langer & Farokhzad – MIT – Harvard CCNE

PNAS (2006) 103: 6315
PNAS (2008) 105: 2586

Comparison of Delivery Profiles for Docetaxel with and without NPs

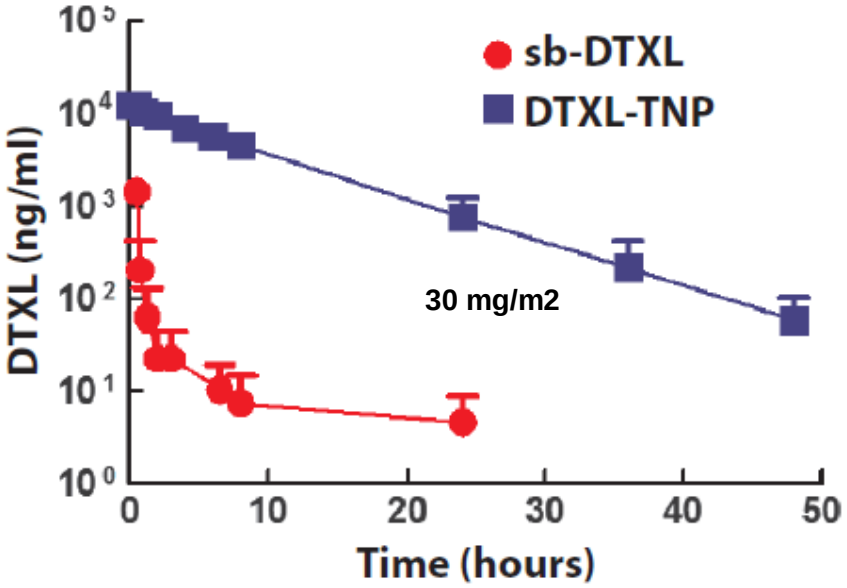


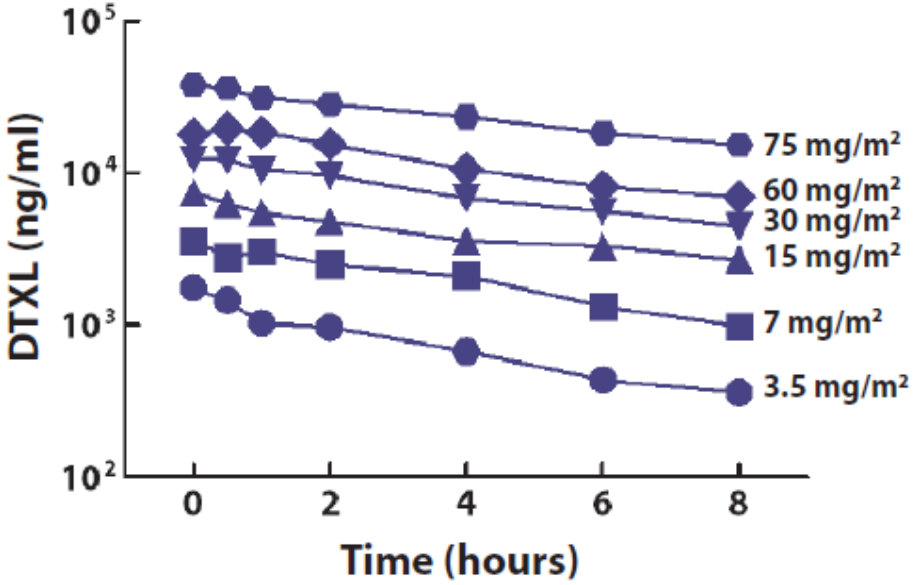




- **Long-circulating particles and controlled drug release provide for well-controlled and differentiated PK profile across species**
- **sb-DTXL elimination from plasma occurs very quickly**

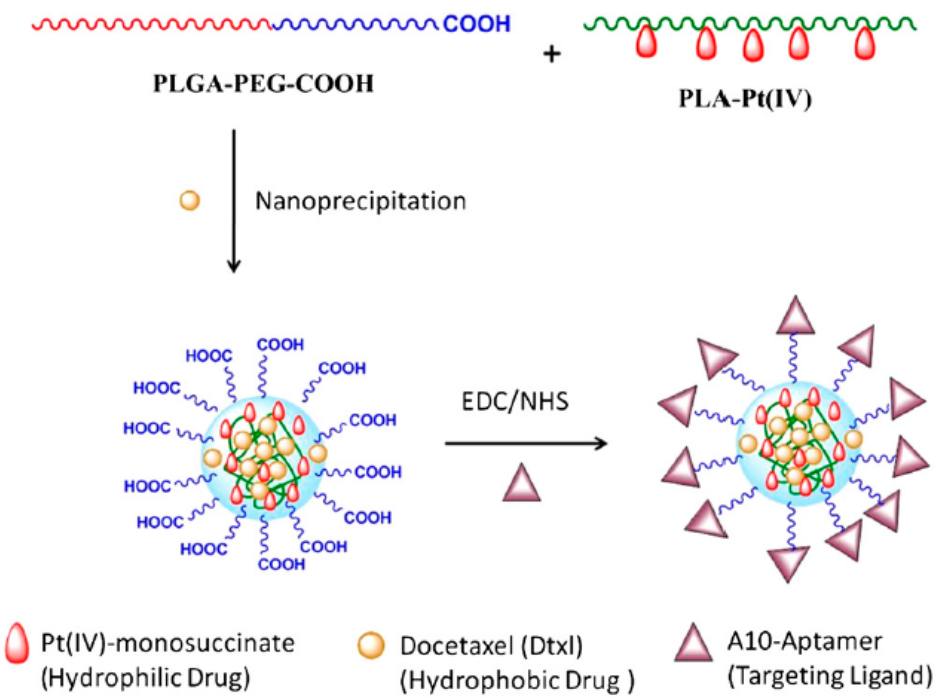
Phase I Clinical Trial – Patient's Data

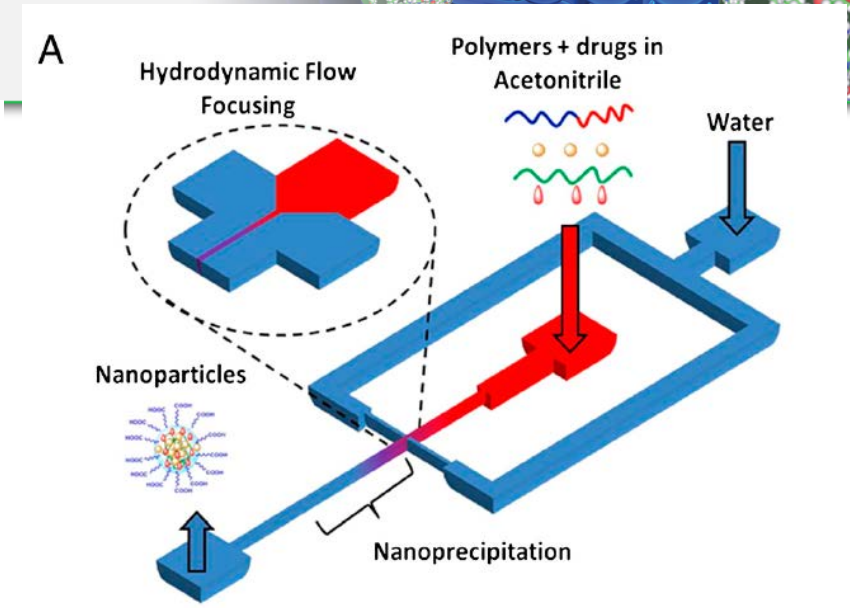




Hrkach J, Von Hoff D, Langer R et al, Science Transl Medicine (2012) 4:1

Combination Therapies Using Nanoparticles



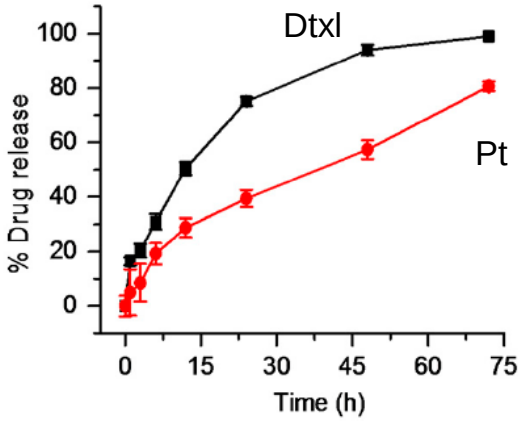


Microfluidics NP synthesis

Multiple drugs in one NP

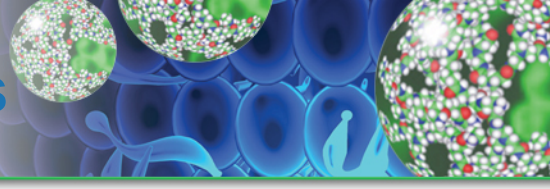
- delivery of a correct ratio of each drug to the target;
- synergistic therapeutic effects;
- ability to control drug exposure temporally

Kolishetti N, Langer R, Farokhzad OC et al., PNAS (2010) 107:17939



In vitro release kinetics in PBS from NPs

Nanotechnology Drug Delivery Strategies



Current

- Using nanoparticles to deliver established chemotherapeutic drugs while enhancing their efficacy
- Existing drugs are readily available and provide a direct, established comparator

Challenge

- Can we ‘resurrect’ drugs which have high potency, but also high toxicity and failed in free form delivery using nanoparticle-based delivery?

Action plan

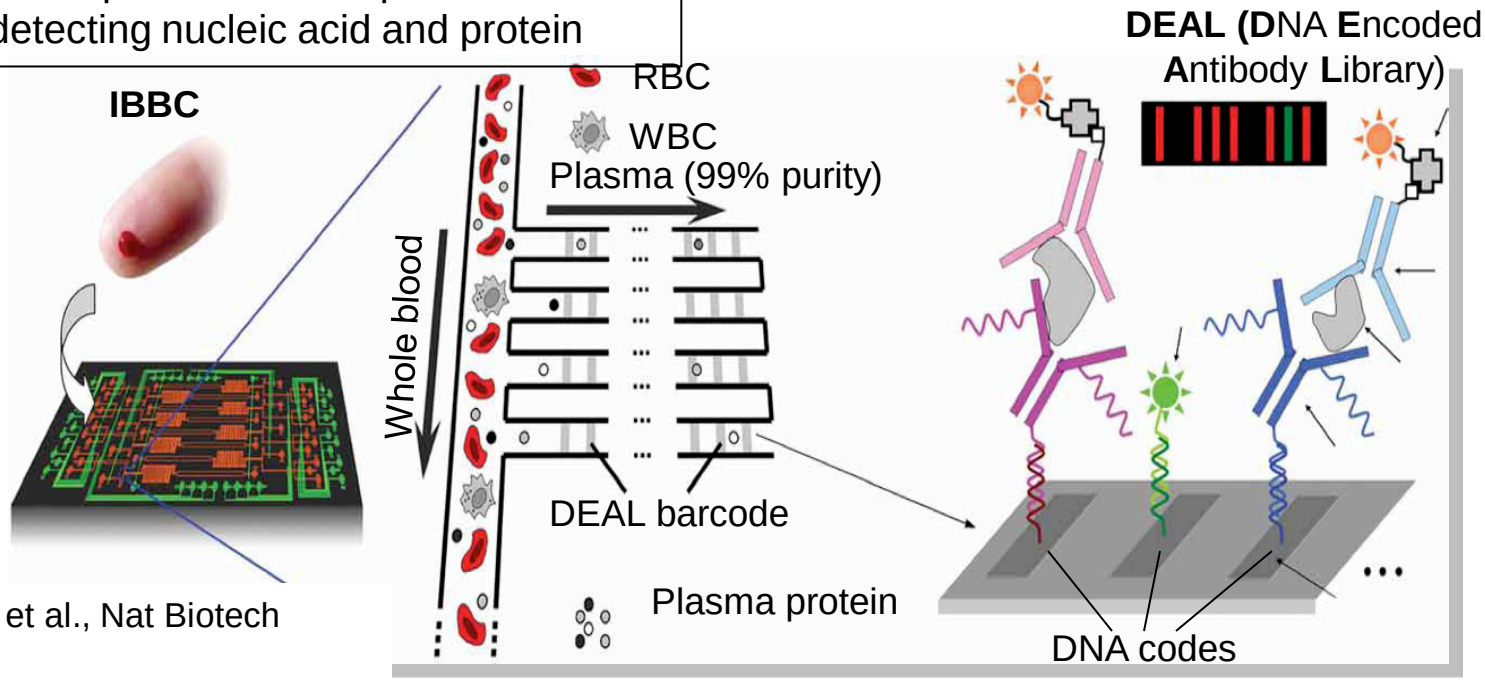
- Proposing a joint development with DCTD to look at few drugs from NCI stockpile.

Integrated Biobarcode Microfluidic Chip

In vitro diagnostics and nanotechnology

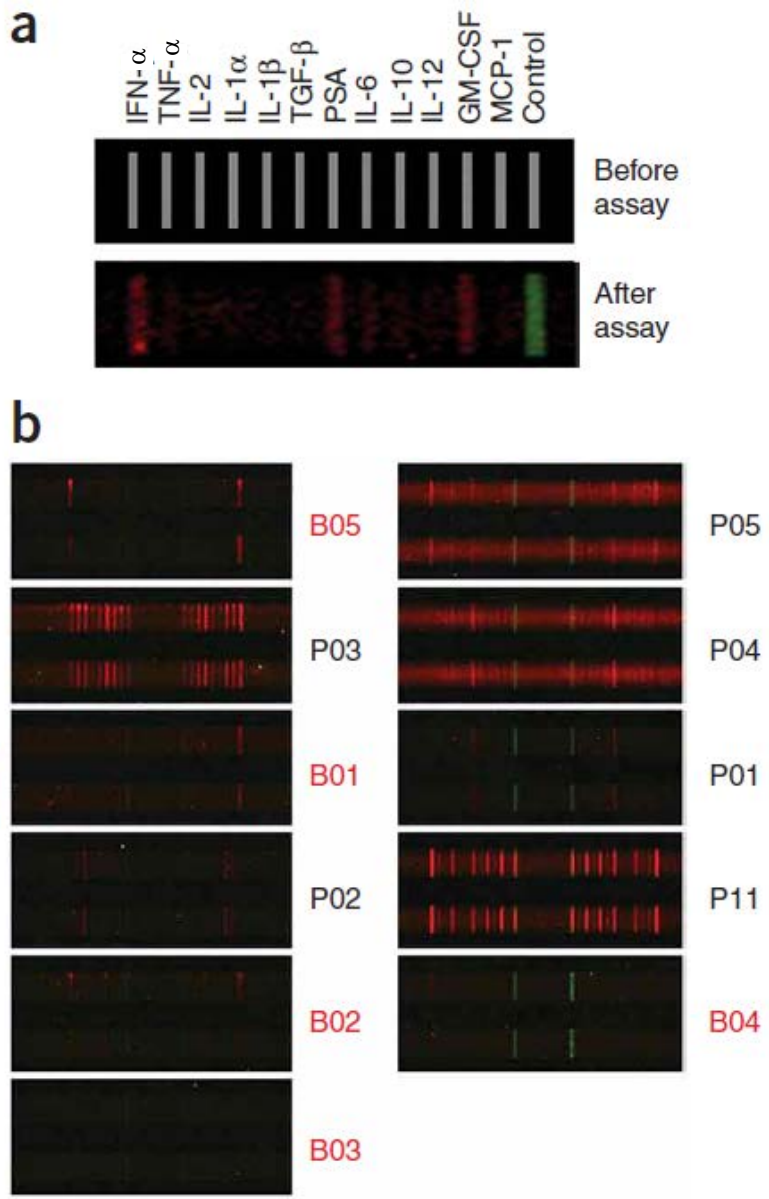
- Modular diagnostics – work with bodily fluids, such as blood, serum, urine, or saliva
- Multiplexing – interrogate several biomolecular signatures at the same time
- Techniques to monitor and capture circulating tumor cells from blood
- Multifunctional capabilities – one platform capable of detecting nucleic acid and protein

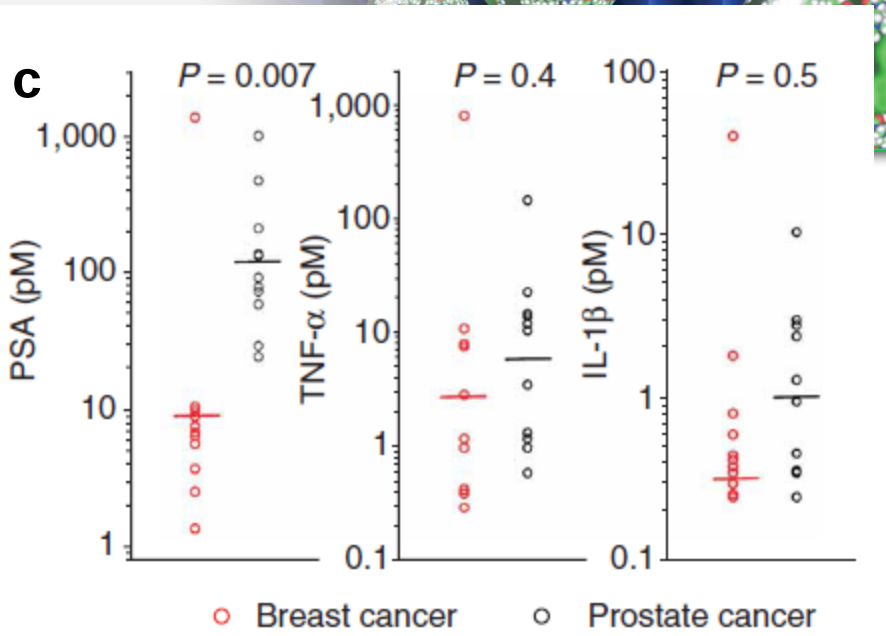
- IBBC - microfluidic device for multiplexed detection of proteins in whole blood sample
- DEAL - single-strain (ss) DNAs bound to antibodies that are labeled with complementary ssDNA oligomers
- Currently tested for molecular and functional analysis of prostate, breast, melanoma, and glioblastoma
- Less than 10 min working time



Fan R, Heath JR et al., Nat Biotech (2008) 26: 1373
Shi Q, Hood L, Mischel PS, Heath JR., Proc Natl Acad Sci U S A (2012) 109:419

Multiplexed Protein Measurements in Clinical Samples

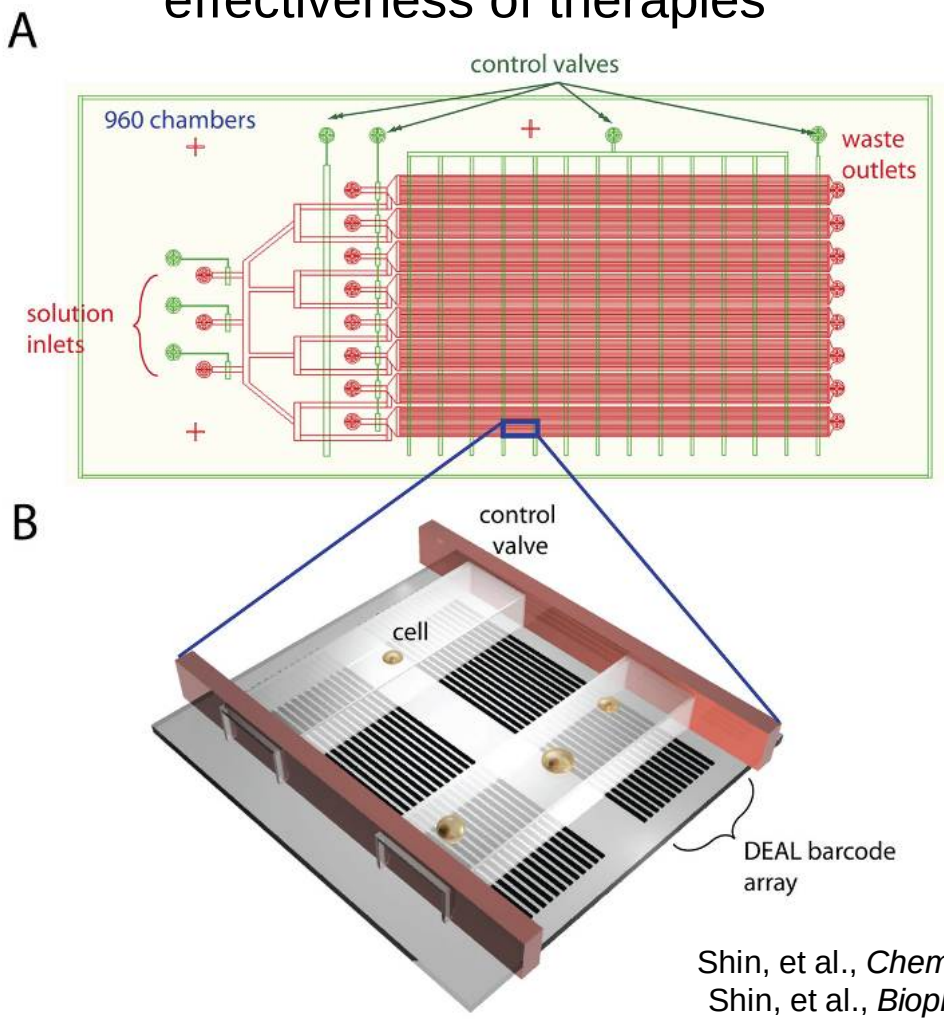




Multiplexed protein measurements of clinical patient sera, (a) Layout of the barcode array used in this study, (b) Representative fluorescence images of barcodes used to measure the cancer marker PSA and 11 cytokines from cancer patient serum samples. B - samples from breast cancer patients; P - samples from prostate cancer patients, (c) Distribution of estimated concentrations of PSA, TNF-α and IL-1β in all serum samples. The horizontal bars mark the mean values.

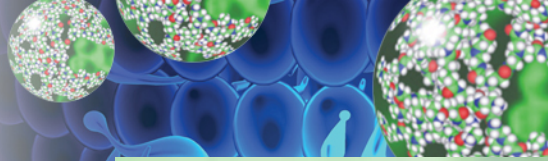
Single Cell Barcode Chip

Monitor secretion of proteins from individual cells to assess effectiveness of therapies



Shin, et al., *ChemPhysChem* 2010 (molecular patterning for these chips)
Shin, et al., *Biophys J* 2011 (macrophage secretome, information theory)
Ma, et al., *Nature Medicine*, 2011 (applied to melanoma immunotherapy patients)

NCI Nanotechnology Alliance Commercial Partners



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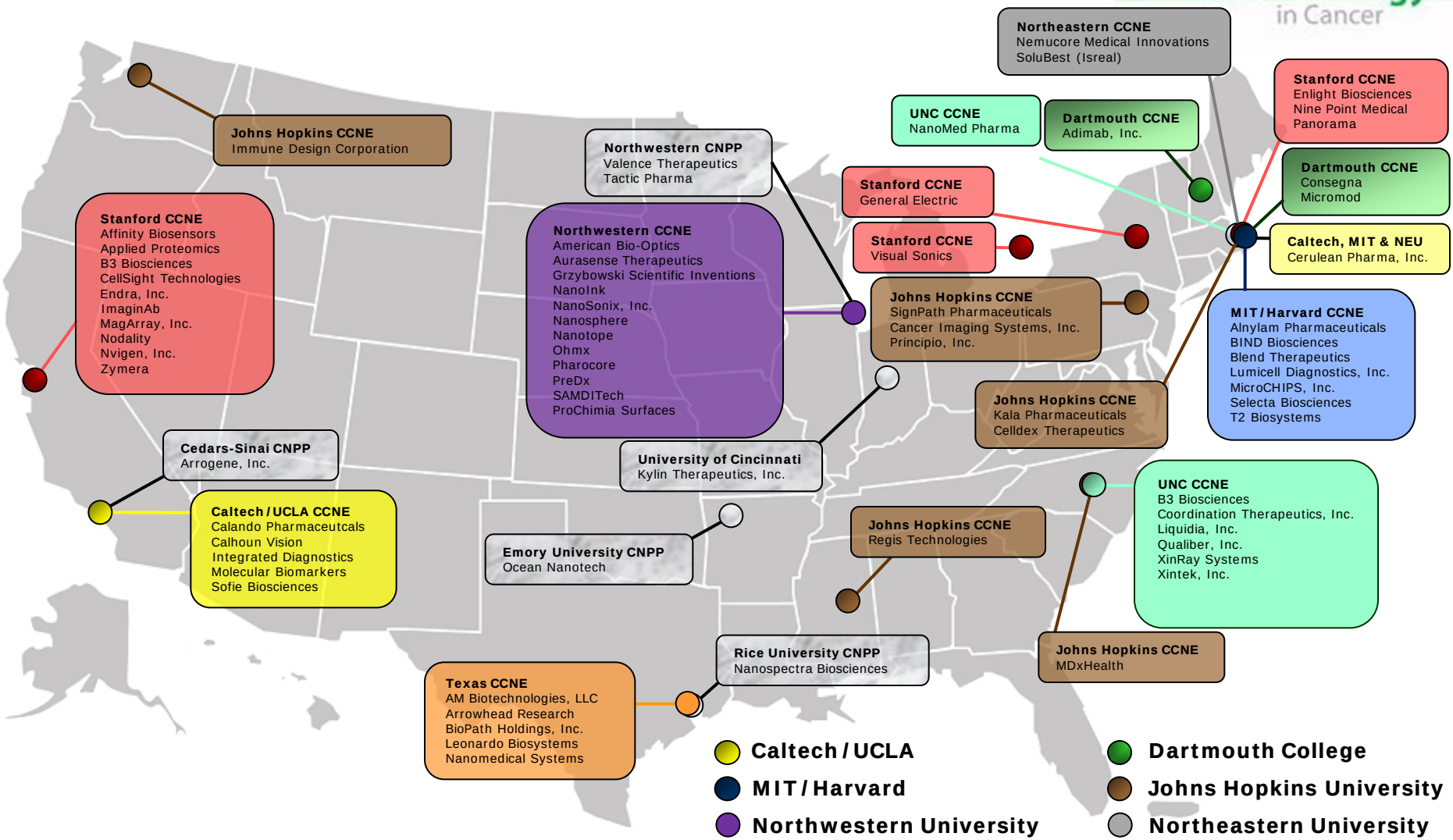
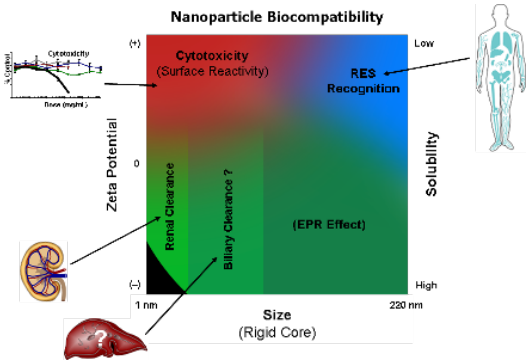


Nanotechnology Characterization Laboratory: Serving the Community



At capacity,
More mature concepts
Work with NIEHS

'09-'12

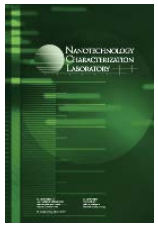
ANNEX 2
NATIONAL CANCER INSTITUTE
NANOTECHNOLOGY CHARACTERIZATION LABORATORY
MATERIAL TRANSFER AGREEMENT
The National Cancer Institute (NCI) Nanotechnology Characterization Laboratory (NCL) has been designed to investigate the use of nanoparticulate material for the advancement of cancer research. This Material Transfer Agreement (MTA) permits the exchange of materials and associated information between NCI and the party defined below as "Provider."

Characterization, SAR studies,
Support of early development

'07-'08

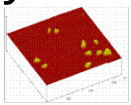
Receipt of materials

'06

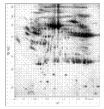


Development of assay cascade

'05



Physicochemical:
–Size
–Shape
–Composition
–Molecular weight
–Surface chemistry
–Identity
–Purity
–Stability
–Solubility

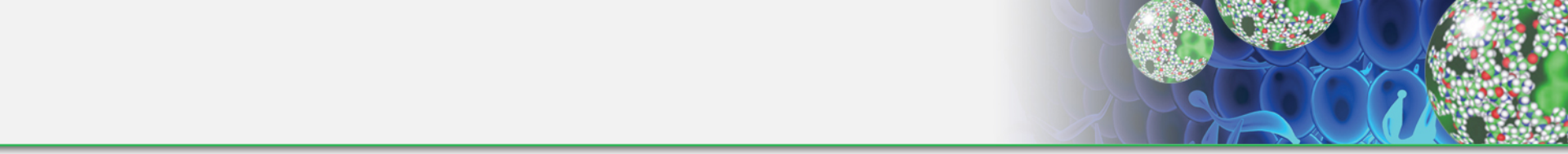


In Vitro:
–Pharmacology
–Blood contact properties
–Immune cell function
–Cytotoxicity
–Mechanistic toxicology
–Sterility

In Vivo:
–ADME
–Safety
–Efficacy

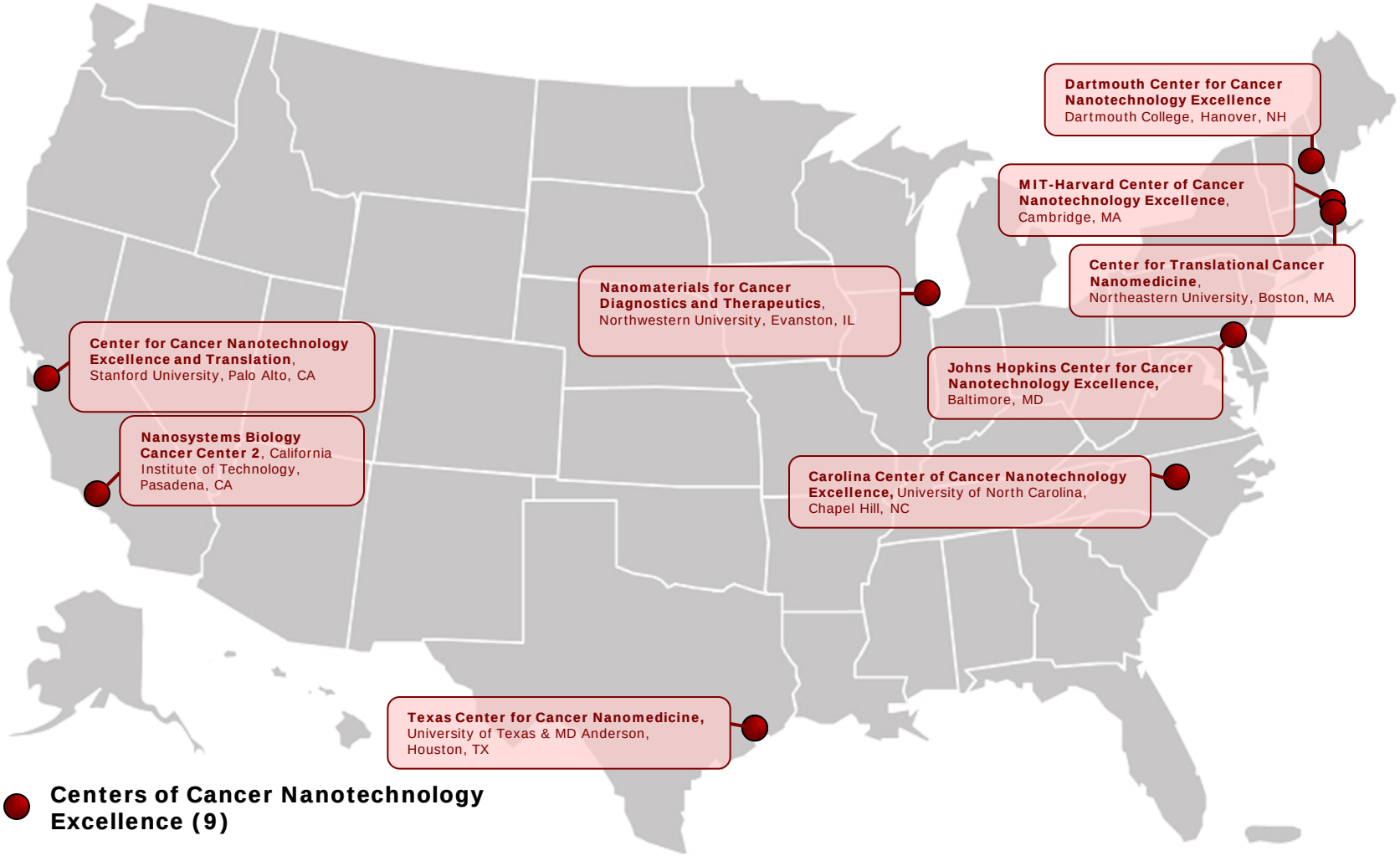
Initiation and planning

'04



Supplemental Slides

Centers of Cancer Nanotechnology Excellence (U54)



NCI Nanotechnology Alliance Awardees 2010