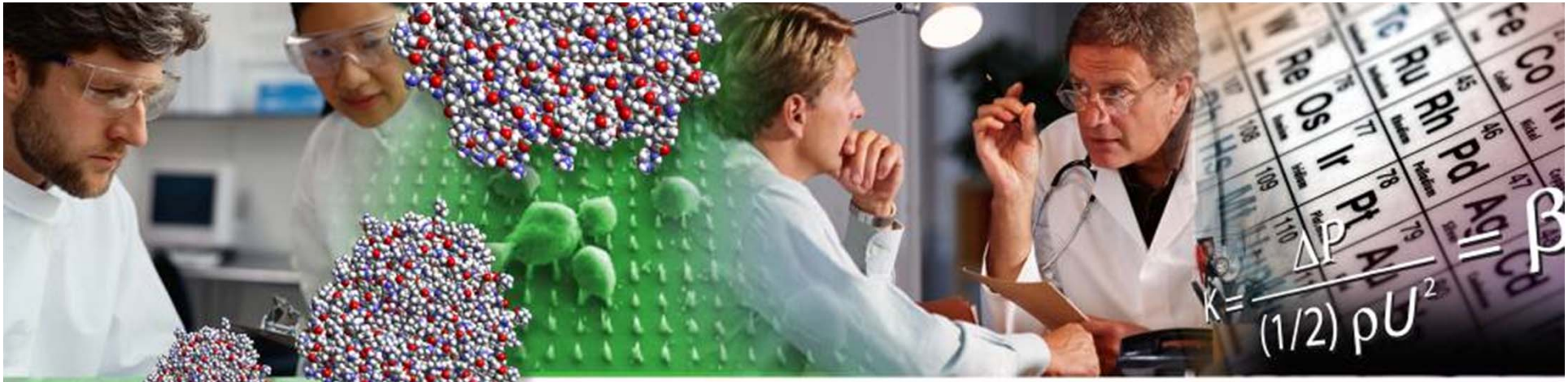


NCI Alliance for Nanotechnology in Cancer: Research Advances and Development of Clinical Applications

Piotr Grodzinski, Ph.D.
Program Director, NCI Nanotechnology Alliance

National Cancer Advisory Board Meeting

June 14, 2006

NCI Nanotech Alliance: Building Interdisciplinary Community

NCI Alliance for Nanotechnology in Cancer

- Form academic and commercial partnerships
- Establish training programs
- Promote interactions among the centers and platform projects
- Leverage existing infrastructure
- Coordinate with other Federal agencies to leverage NCI funds and creates synergies
- Pre-qualify new materials and informs standards through the Nanotechnology Characterization Laboratory
- Reduce the risk of investment in new products

Governance of CCNEs

NCI Alliance for Nanotechnology in Cancer

- Coordinating and Governance Committee (CGC) is the operational governing board responsible for overall coordination of the CCNE program.
- CGC meets twice a year to assess scientific progress, identify new research opportunities, establish priorities, consider policy recommendations, and discuss strategy.
- CGC membership includes at least one member from each CCNE, NCI Program Director (Piotr Grodzinski), and representative from public advocacy group (Wayland Eppard).
- CGC co-chairs: Chad Mirkin (Northwestern), Jonathan Simons (Emory), Piotr Grodzinski (NCI). Chair positions will be rotated every 18 months.

Centers of Cancer Nanotechnology Excellence
Programmatic Areas

NCI Alliance for Nanotechnology in Cancer

		Programmatic Areas					
PI	**Institutions**	**Molecular Imaging & Early Detection**	***In vivo* Imaging**	**Reporters of Efficacy**	**Multifunctional Therapeutics**	**Prevention & Control**	**Research Enablers**
Langer	MIT/Harvard/MGH	X		X	X		X
Nie	Georgia Tech/Emory		X	X	X		X
Esener	UCSD/Burnham	X			X	X	X
Heath	CalTech/UCLA	X				X	X
Juliano	UNC/Duke	X	X		X		X
Wickline	WUSTL/Illinois		X		X		X
Mirkin	Northwestern/UIUC	X		X		X	X
Gambhir	Stanford	X	X			X	X

Centers of Cancer Nanotechnology Excellence
Characteristics

NCI Alliance for Nanotechnology in Cancer

- Technologies represented **thoroughly address the six programmatic areas** of the Alliance for Nanotechnology in Cancer
- Projects supported comprise a **balanced mix of high risk/innovative and lower risk/evolutionary** approaches
- **Multidisciplinary teams** of technologists and biologists
- Centers are **geographically distributed** across the country
- Centers effectively **leverage** existing infrastructure
- Centers cover a **broad range of cancer and organ-specific** techniques

NCI Alliance for Nanotechnology in Cancer

Recent Technology Developments and Their Clinical Significance

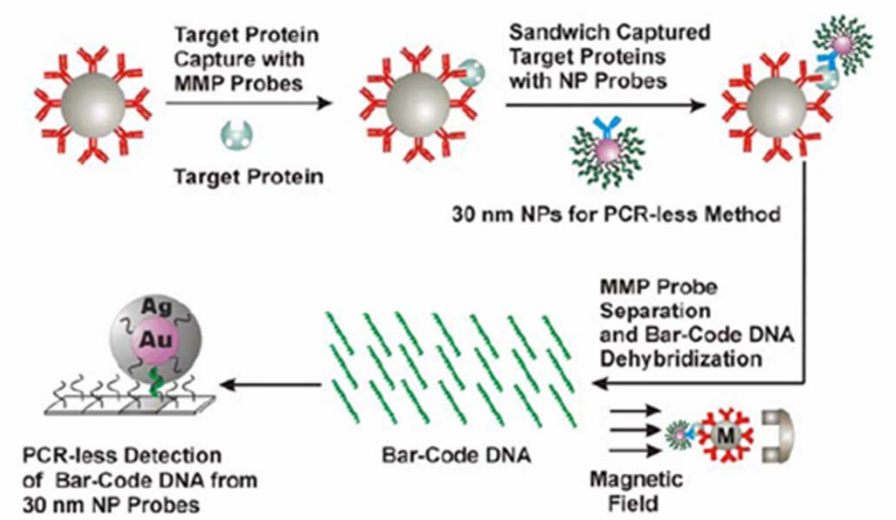
- High sensitivity, multiplex detection for diagnosis and recurrence monitoring
- New contrast agents for in vivo imaging
- Targeted, nanoparticle-based delivery of docetaxel

CCNE: Northwestern

Program Area: Early Detection

Bio-barcode Detection of PSA

NCI Alliance for Nanotechnology in Cancer



- High sensitivity (two orders of magnitude improvement) assay for recognition and recurrence monitoring of prostate cancer
- Clinically accepted conventional assays for detecting PSA have sensitivity limits of ~ 3 pM

Stoeva, Thaxton, Mirkin, Multiplexed DNA Detection with Biobarcoded Nanoparticle Probes, Angew Chem Int 45, 3303 (2006)

Cheng, Cuda, Bunimovich, Gaspari, Heath, Mirkin, Ferrari et al., Nanotechnologies for biomolecular detection and medical diagnostics, Curr Opin Chem Biol. 10, 11 (2006)

CCNE: Northwestern

Program Area: Early Detection

Biomolecule Detection Technologies

NCI Alliance for Nanotechnology in Cancer

Biomolecule Detection Technology

Concentration	Molecule/Drop	Detection/ Targets/Disease
10^{-3}- Millimolar	Quadrillions	Colorimetric/Enzymatic Chemistry Blood Sugar (Diabetes)
10^{-6}- Micromolar	Trillions	ELISA & Chemiluminescence Troponin, CK-MB, BNP, βHCG
10^{-9}- Nanomolar	Billions	
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	

CCNE: Emory-Georgia Tech

Program Area: Molecular Imaging and Early Detection

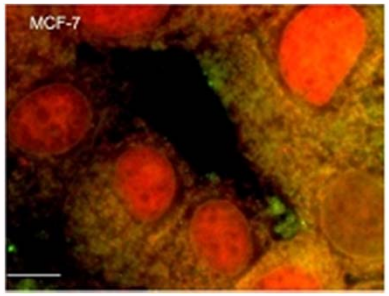
Quantification and Comparison of Breast Cancer Biomarkers Using Ab-Conjugated QDs

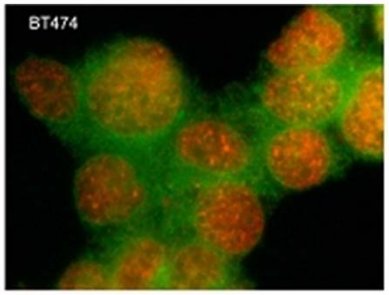
NCI Alliance for Nanotechnology in Cancer

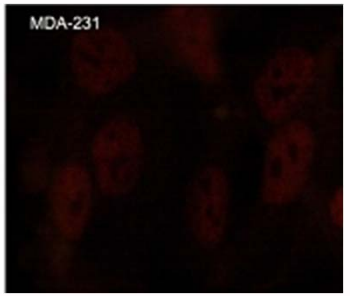
HER2/neu

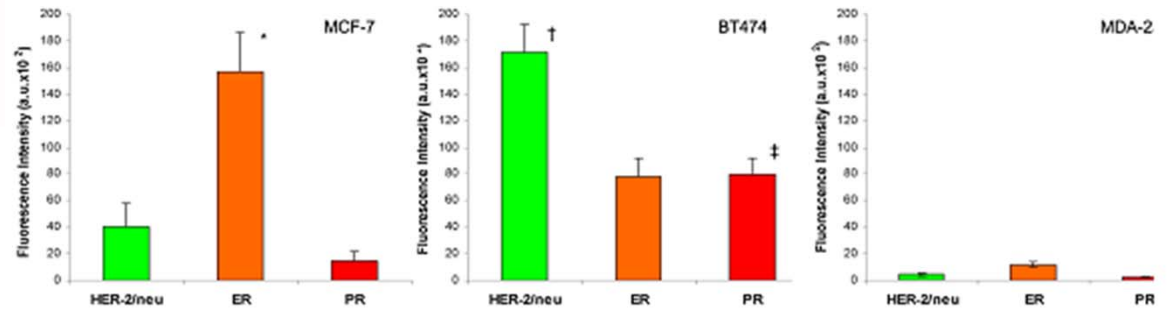
Estrogen receptor

Progesterone receptor









- ER, PR, and HER2 can be detected using multiplex QDs simultaneously on specimens of breast cancer cell lines
- ER, PR and HER2 detected using QD-Abs can be quantified using spectrometry
- Detection/quantification of ER, PR and HER2 using QD-Abs correlated well with standard methods (IHC and Western Blotting)

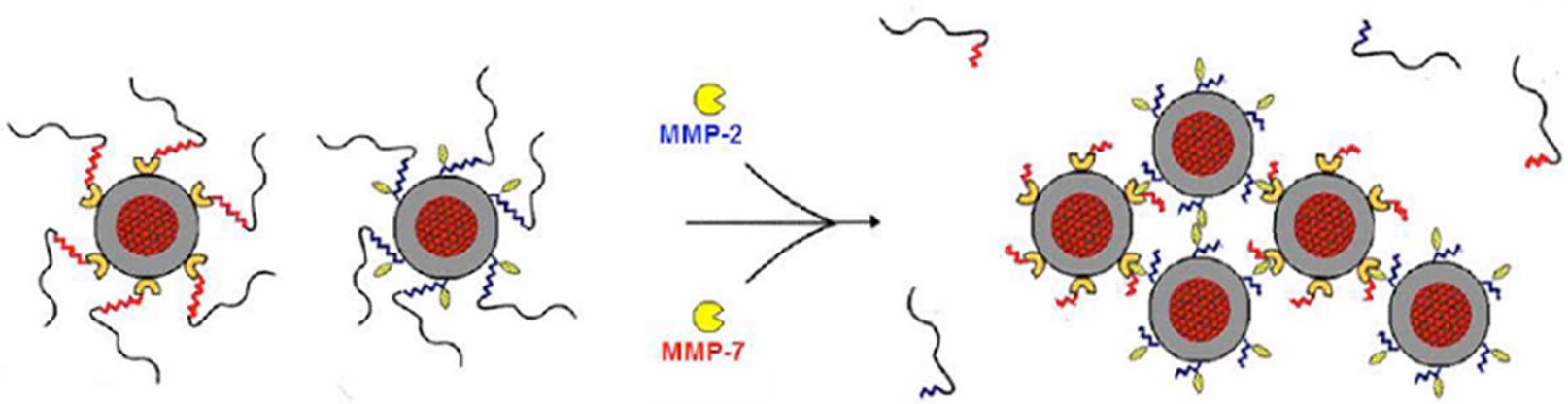
O'Regan et al., submitted to *PNAS*

CCNE: UCSD

Program Area: Early Diagnostics/*In Vivo* Imaging

MRI Detection of Tumor Derived Cells via Proteolytic Actuation of Nanoparticle Assembly

NCI Alliance for Nanotechnology in Cancer



Pegylated particles do not assemble

After MMP cleavage assembly occurs

- Nanoparticles assemble only in the presence of two enzymes associated with tumorigenesis: 1) MMP2 – associated with tumor metastasis, invasion, and angiogenesis; 2) MMP7 - promotes an anti-apoptotic phenotype in the tumor milieu
- Initial restriction of assembly is achieved through attachment of MMP2 peptide-PEG or the MMP7 peptide-PEG polymers to biotin and neutravidin particles, respectively

Nanoassemblies provide for:

Magnetic susceptibility

↓

T2 relaxivity

↓

Diffusivity

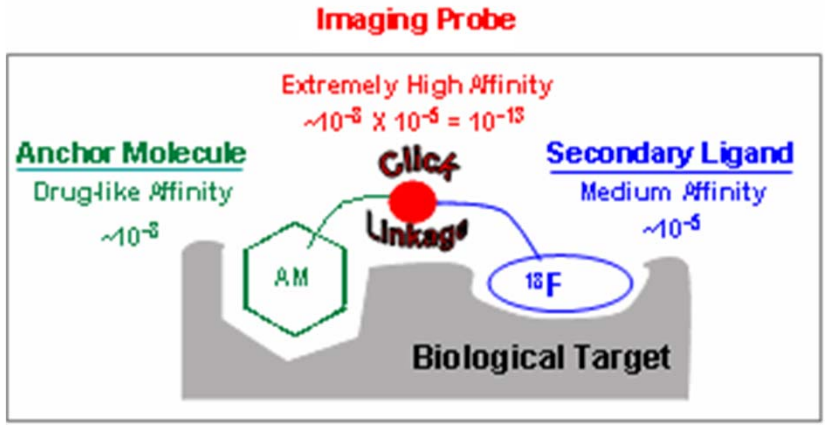
Harris, Ruoslahti, Bhatia et al., Proteolytic Actuation of Nanoparticle Self-Assembly Angew. Chem. Int. 45, 3161 (2006)

E. Ruoslahti, S. Bhatia

CCNE: Caltech
Program Area: Research Enabler
Production of Molecular Probes with *in situ* Click Chemistry

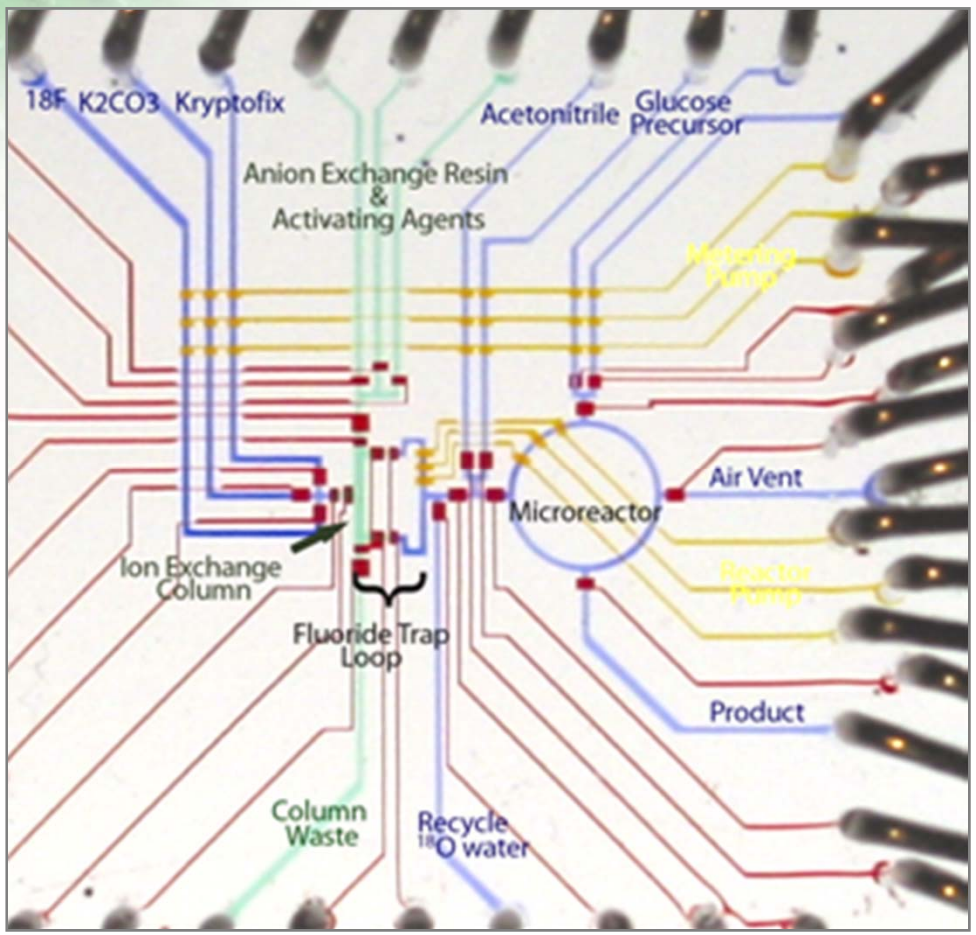
NCI Alliance for Nanotechnology in Cancer

- **Extremely high affinity for disease-related biological targets:**
  - Affinities in the range of 10^{-9} to 10^{-14}
- **High specificity for disease targets:**
  - Imaging probes designed by the target for the target (>99% yield)
- **Small molecules:**
  - Imaging probes with access to surface receptors, cells and nucleus
- **Reliable synthesis:**
  - Systematic, scalable and rapid attachment of radiolabel probes on integrated microfluidic chips



CCNE: Caltech
Program Area: Research Enabler//*In Vivo* Imaging
Chemical Reaction Circuit for Preparing Radiolabeled Molecular Imaging Probes

NCI Alliance for Nanotechnology in Cancer



Chemical Synthesis Steps Executed on Chip

- Ion exchange
- Anhydrous reactions
- Chemistry at elevated temperature and pressure
- Solvent exchange
- Product elution

Generates [^{18}F]FDG

- With improved radio-chemical yield
- In 1/3 the time compared to traditional synthesis box

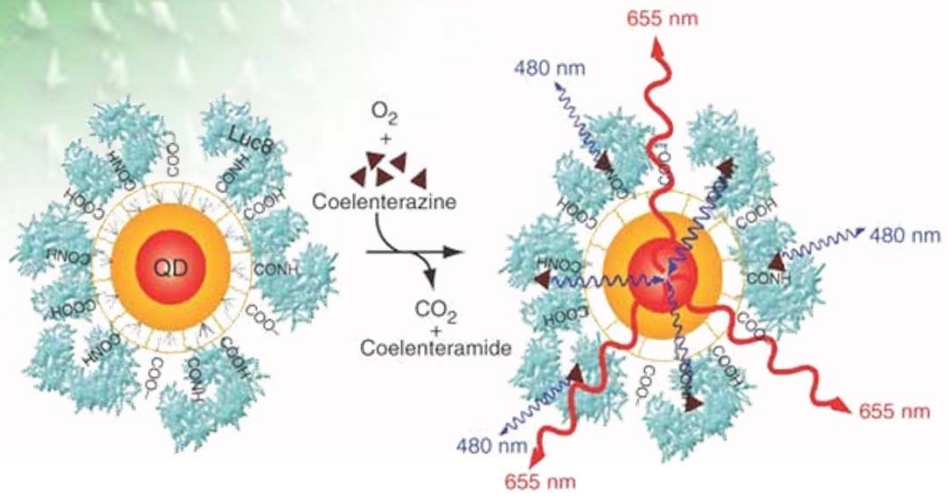
Lee, Elizarov, Heath, Phelps, Quake, Tseng et al, Multistep synthesis of a radiolabeled imaging probe using integrated microfluidics, Science 310, 1793 (2005)

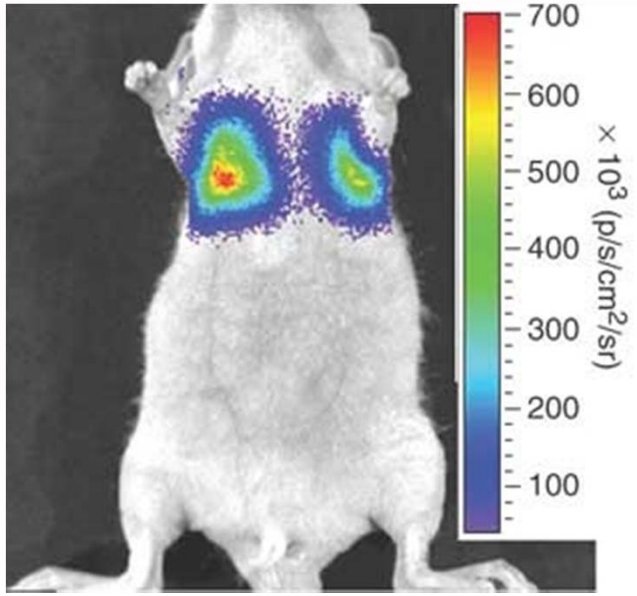
CCNE: Stanford

Program Area: *In Vivo* Imaging

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

- Imaging of C6 glioma cells labeled with a quantum dot conjugate show signal in deep tissue, improved sensitivity, and potential for multiplexing without the need for external illumination

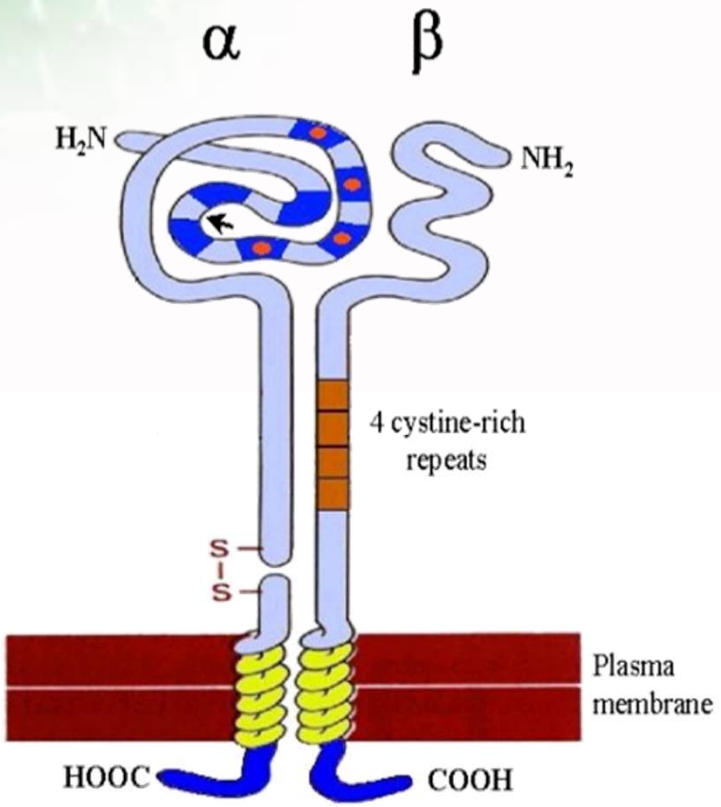
So, Gambhir, Rao et al., Self-illuminating quantum dot conjugates for in vivo imaging, Nat. Biotechnol. 24, 339 (2006)

CCNE: Siteman

Program Area: Multifunctional Therapeutics

Integrin vasculature targeting

NCI Alliance for Nanotechnology in Cancer



- $\alpha_v\beta_3$ targeted paramagnetic nanoparticle agent for diagnostic imaging and therapy is moving to clinical trial
- Integrin $\alpha_5\beta_1$ is an important adhesion molecule which regulates endothelial cell migration and survival
- Evaluate synergy of $\alpha_v\beta_3$ and $\alpha_5\beta_1$ targeted nanoparticles

Schmieder, Winter, Wickline, Lanza et al., MR molecular imaging of melanoma angiogenesis with $\alpha_v\beta_3$-Targeted paramagnetic nanoparticles. Magn. Reson. Med. 53, 621 (2005)

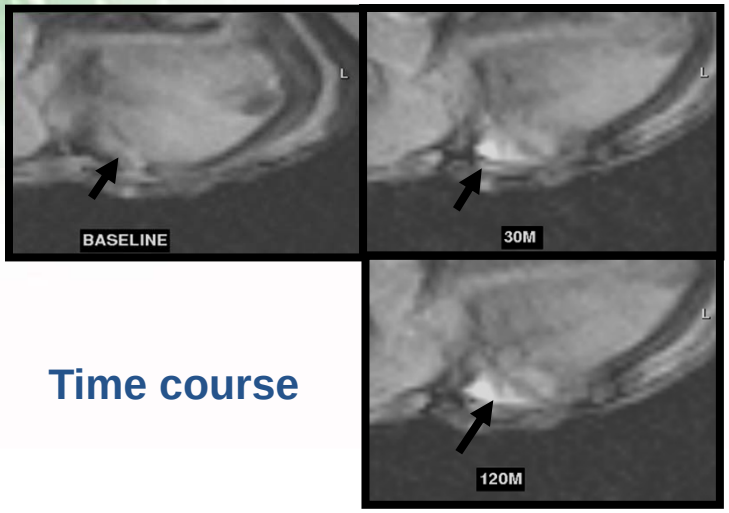
CCNE: Siteman

Program Area: Multifunctional Therapeutics

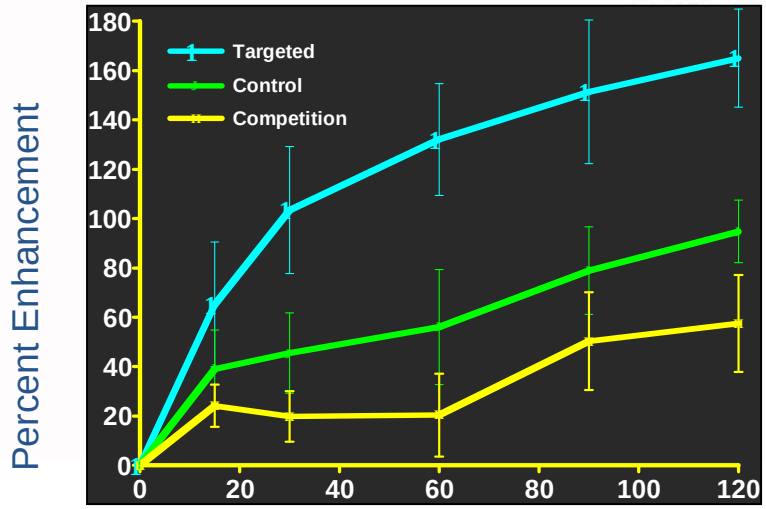
Targeted Imaging and Therapeutic Impact

NCI Alliance for Nanotechnology in Cancer

Imaging

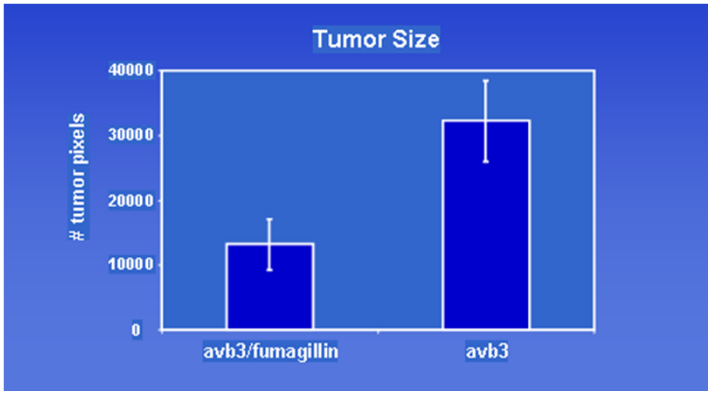


Time course

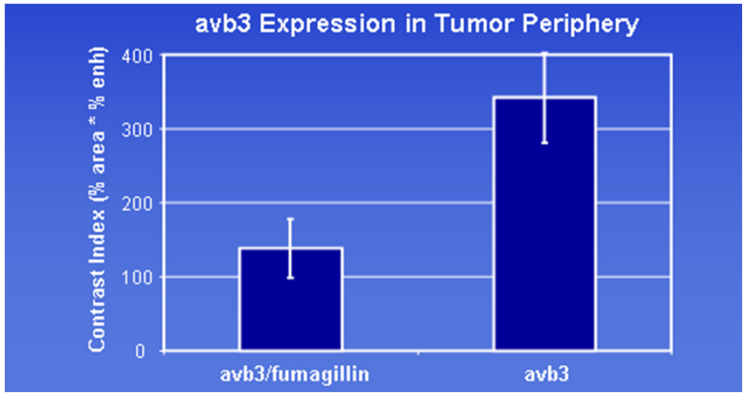


Treatment

Serial (3) Treatments of $\alpha_v\beta_3$-fumagillin nanoparticle decreases tumor size
60% smaller in Fumagillin group (p = 0.026)



Serial (3) Treatments of $\alpha_v\beta_3$-fumagillin nanoparticle decreases peripheral tumor neovascularity
60% lower in Fumagillin group (p = 0.018)

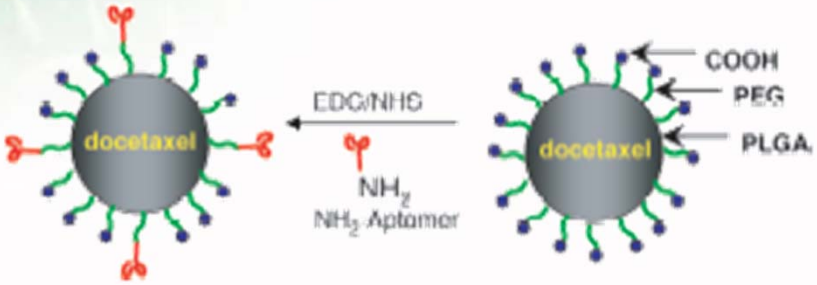


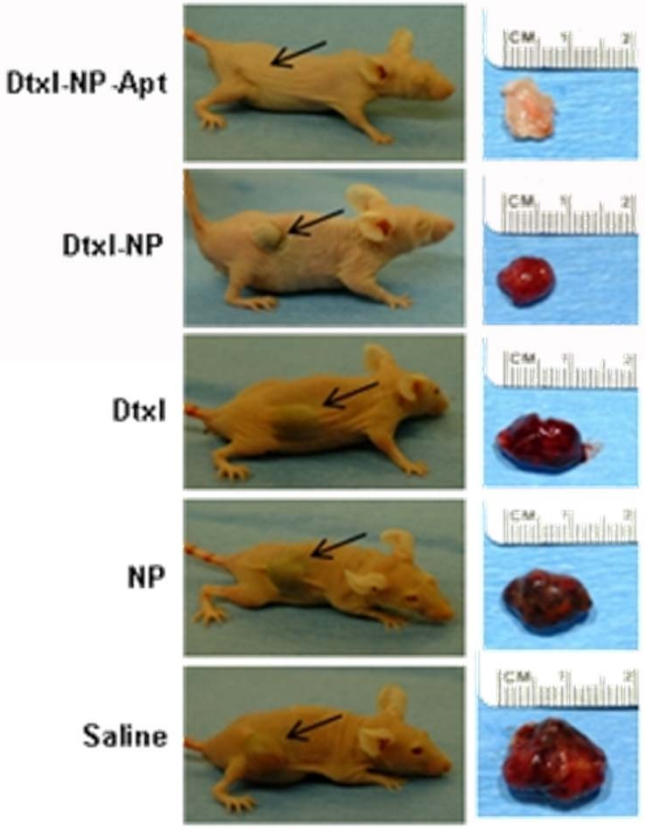
CCNE: MIT-Harvard

Program Area: Multifunctional Therapeutics

Docetaxel-Encapsulated Pegylated PLGA Nanoparticle-Aptamer Conjugates

NCI Alliance for Nanotechnology in Cancer





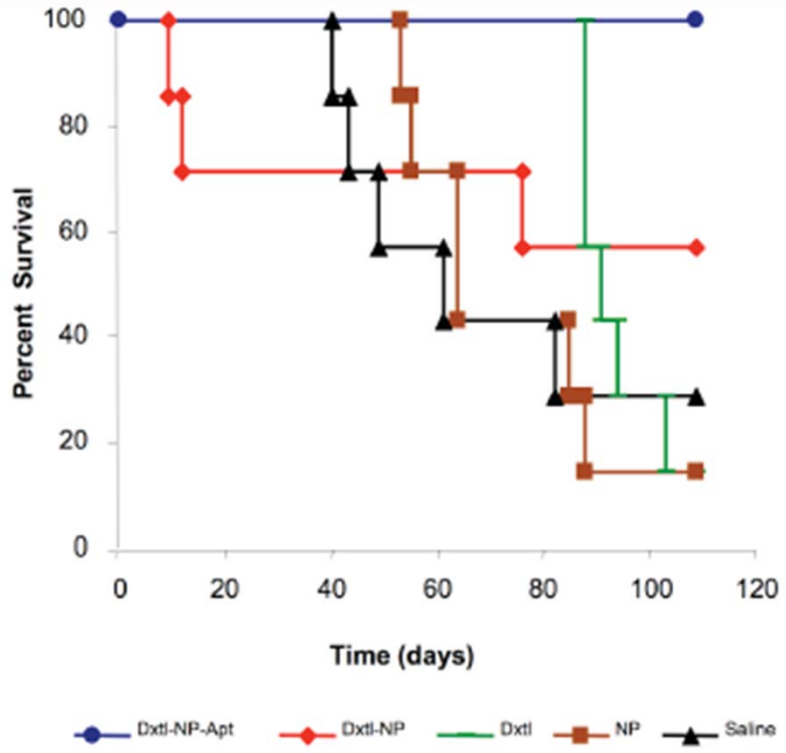
Nanoparticle-Aptamers conjugates have been developed for Prostate Specific Membrane Antigen (PSMA) and show greater efficacy in a xenograft mouse model than non-targeted nanoparticles

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

CCNE: MIT-Harvard
Program Area: Multifunctional Therapeutics
Clinical Impact

NCI Alliance for Nanotechnology in Cancer

- Demonstrates the ability to target prostate cancer cells and deliver a therapeutic payload over an extended period of time
- Approach has shown increased therapeutic index relative to the non-targeted therapy and strategically utilizes components (polymer, drug, targeting agent) that will facilitate FDA approval
- Localized cancer therapy with reduced toxicity
- Next steps: large animal studies



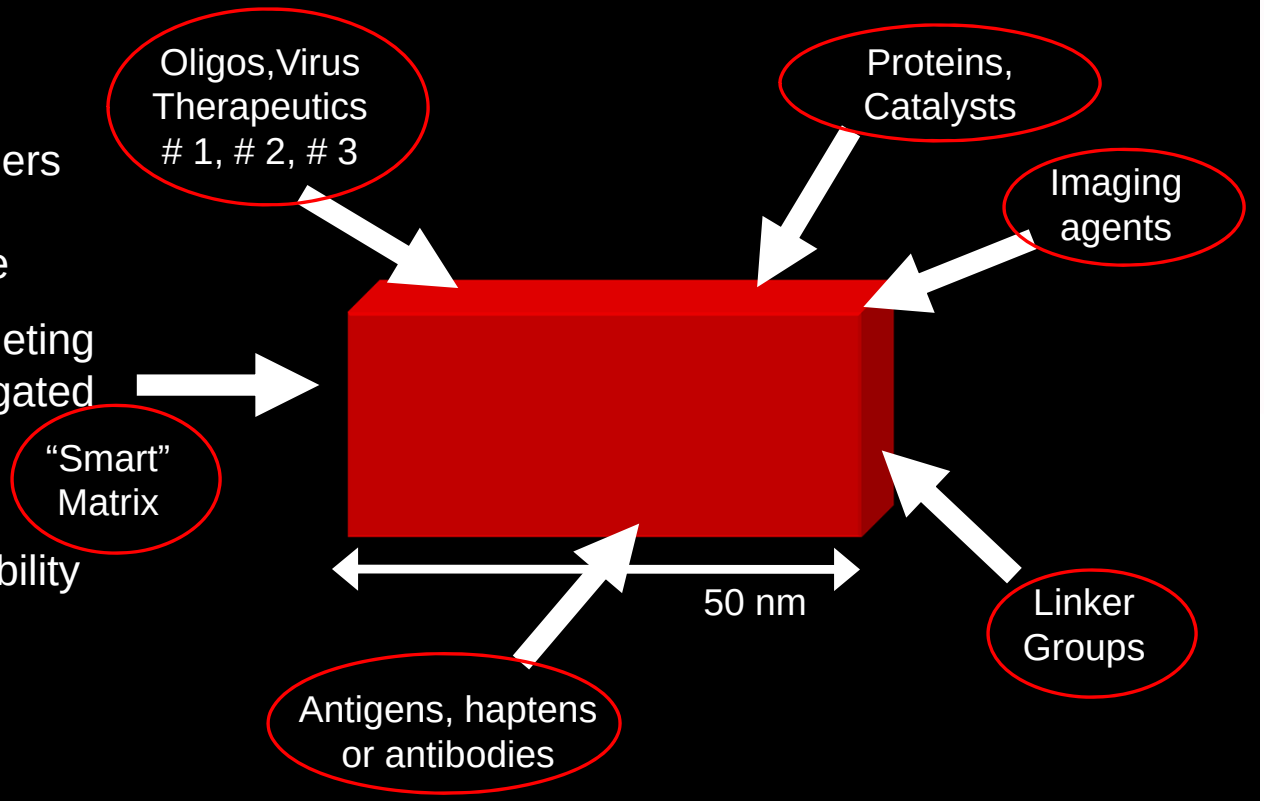
CCNE: Carolina

Program Area: Multifunctional Therapeutics and *In Vivo* Imaging

Flexible PRINT Method for Particle Synthesis

NCI Alliance for Nanotechnology in Cancer

- Biocompatible and biodegradable polymers are amenable to the processing technique
- A wide variety of targeting agents can be conjugated to the surface of the particles
- Drugs with poor solubility can be incorporated



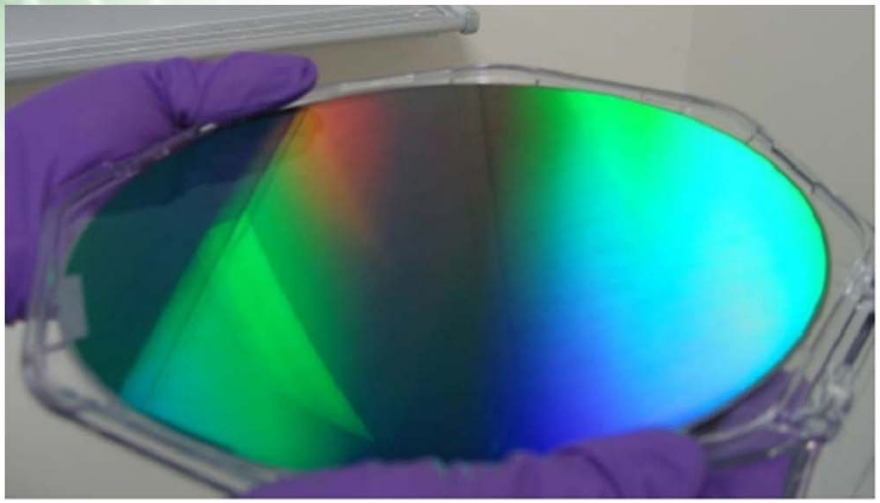
Rolland, DeSimone et al., Direct fabrication and harvesting of monodisperse, shape-specific nanobiomaterials, J Am Chem Soc.127 10096 (2005)

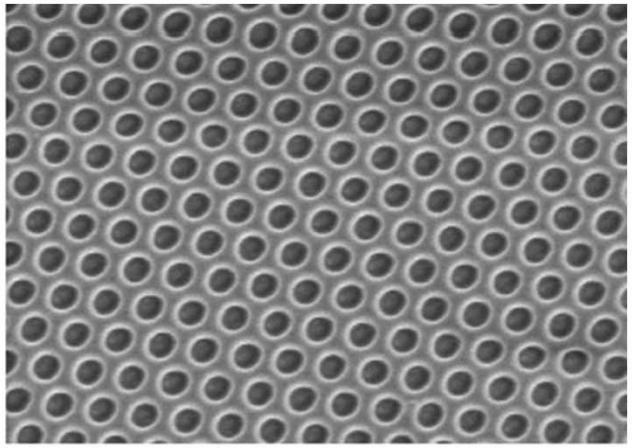
CCNE: Carolina

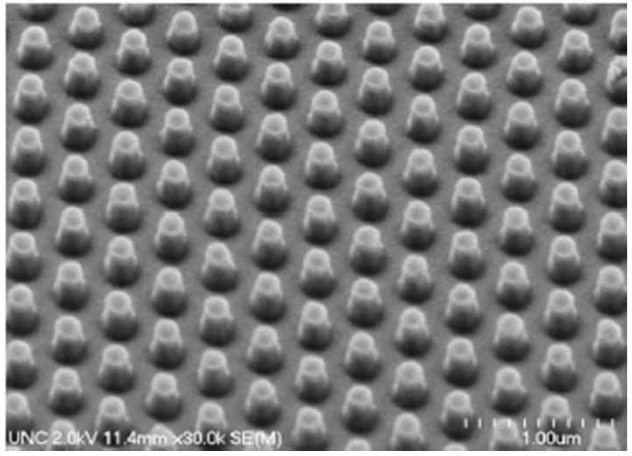
Program Area: Multifunctional Therapeutics and *In Vivo* Imaging

Organic Nanoparticles via PRINT (Particle Replication in Non-wetting Templates)

NCI Alliance for Nanotechnology in Cancer







- 8 inch wafer, canonical posts, each post is 160 nm at top tapered to 200 nm at bottom to facilitate harvesting;
- Generates 8 mgs / wafer
- Micrographs show nanoparticles on medical adhesive harvesting layer at 45^{o} angle.

Non-wetting substrate and PFPE mold enable gentle fabrication of organic materials; rigorous control of shape, size, and chemical structure

Progress in 2007

NCI Alliance for Nanotechnology in Cancer

- Develop uniform strategies towards technology transfer and data sharing among the centers
- Propagate caLAB software model for data management
- Anticipated path towards product and clinical use:
  - Clinical trials of bio-barcode assay for prostate cancer detection
  - Human clinical trials of integrin-targeted nanoparticles loaded with gadolinium
  - Human clinical trials of integrin-targeted nanoparticles loaded with fumagilin for blocking of tumor induced angiogenesis
  - Large animal studies of aptamer-targeted nanoparticles for the treatment of prostate cancer
  - Commercialization of “smart” nanoparticle platform technology and selection of pharmaceutical company partner for further development

The Alliance Website: http://nano.cancer.gov

NCI Alliance for Nanotechnology in Cancer

- Timely reports of scientific advances
- Accessible, comprehensive info
- Teaming site for potential collaborations
- Secure site for Alliance communications