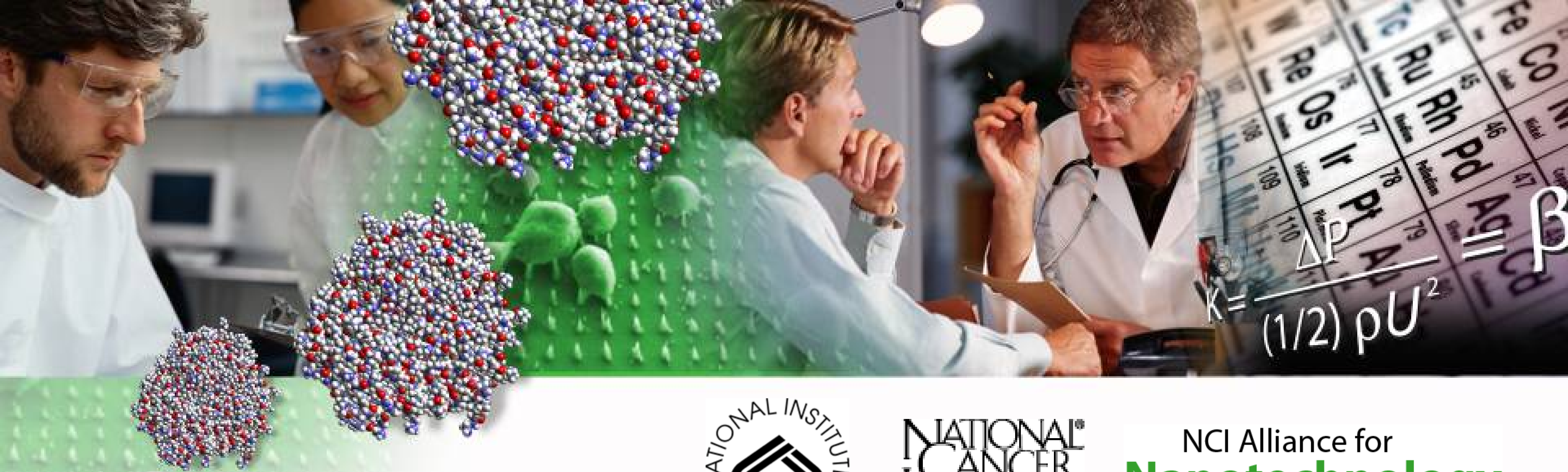

NATIONAL INSTITUTES OF HEALTH

NATIONAL CANCER INSTITUTE

NCI Alliance for **Nanotechnology** in Cancer

The NCI Nanotechnology Alliance for Cancer: Making Personalized Cancer Medicine a Reality

Policy Issues in Nanotechnology and Oncology: National Cancer Policy Forum Workshop

July 12-13, 2010

Anna D. Barker, Ph.D.
National Cancer Institute

OVERVIEW

NCI Alliance for Nanotechnology in Cancer

- *Does cancer represent a healthcare crisis – and why is it so difficult to intervene at all levels?*
- **What will personalized approaches to cancer intervention require?**
- **Why nanotechnology for cancer?**
- **The NCI's Alliance for Nanotechnology and Cancer – enabling a shift to personalized cancer medicine!**
- **The Future!**

The Future: Molecular Oncology

NCI Alliance for Nanotechnology in Cancer

Advances in Molecular Research and Technologies

The Past Century	21st Century
Established system to treat established disease – a treatment/therapeutic focus (in cancer often too late)	Shift to targeted Interventions for prevention and treatment – shift in focus to early detection and prevention
Morphologic and pathologic diagnosis – drove treatment	Driven by the molecular characterization of disease – mechanistic understanding of pathways and processes
Expensive in all respects – not sustainable in 21st century	Evidence based – preserves human and financial capital – sustainable – Health becomes major national asset
Healthy population not a focus as a major national advantage/asset	

Does cancer represent a healthcare crisis – and why is it so difficult to intervene at all levels?

Healthcare Realities

NCI Alliance for Nanotechnology in Cancer

- Healthcare spending in 2009 projected - $2.5 trillion
- Rose one percentage point last year – to represent 17.9% of U.S. economy (largest increase since CMS began tracking)
- Increases expected to continue through 2018 (anticipated to reach $4.4 trillion - ~20% of economy) (public spending could account for 50% of total)
- Investment in private healthcare spending declining – (3.9% last year – 15 year low)
- Prescription drug spending slowing – 3.5% in 2008 vs. 4.9% in 2007
- Five “targeted” oncology drugs were in the $1B class in 2007 – large numbers in pipelines

By Nearly All Measures Cancer Already Represents a Healthcare Crisis

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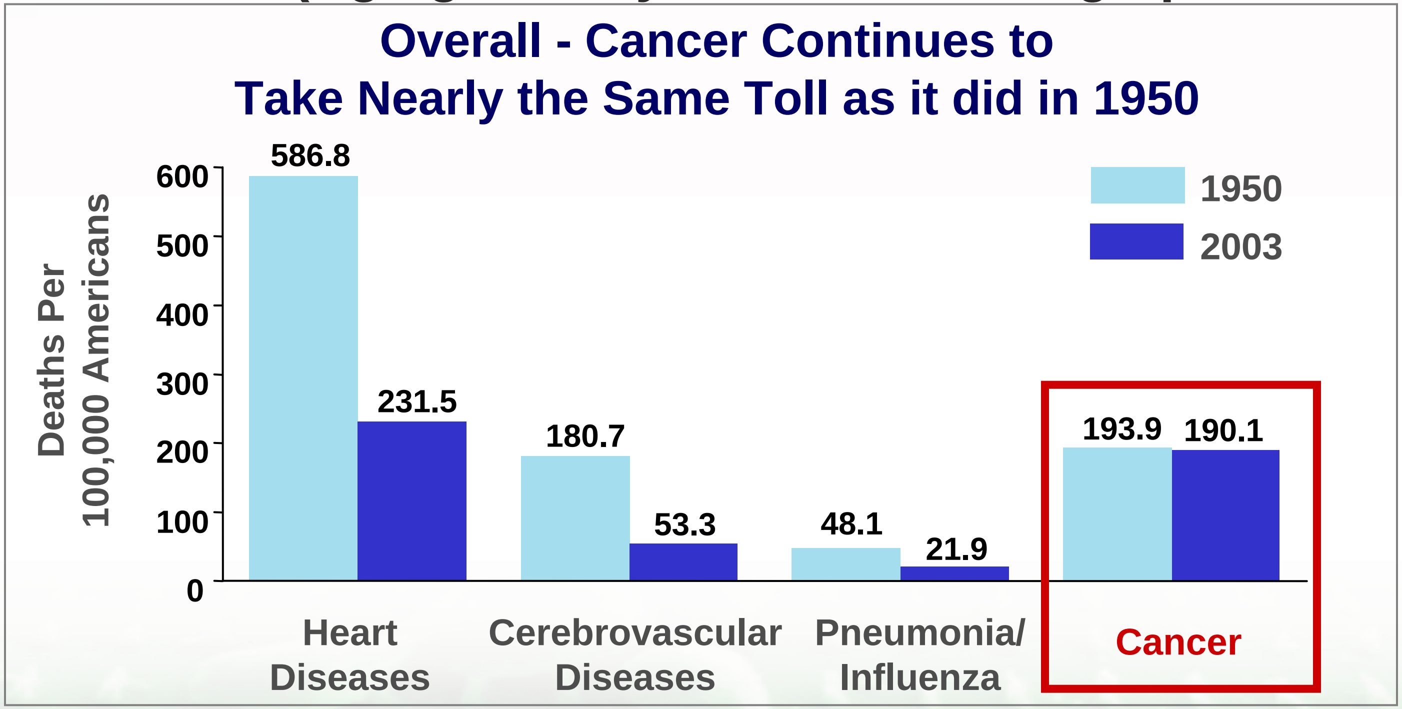
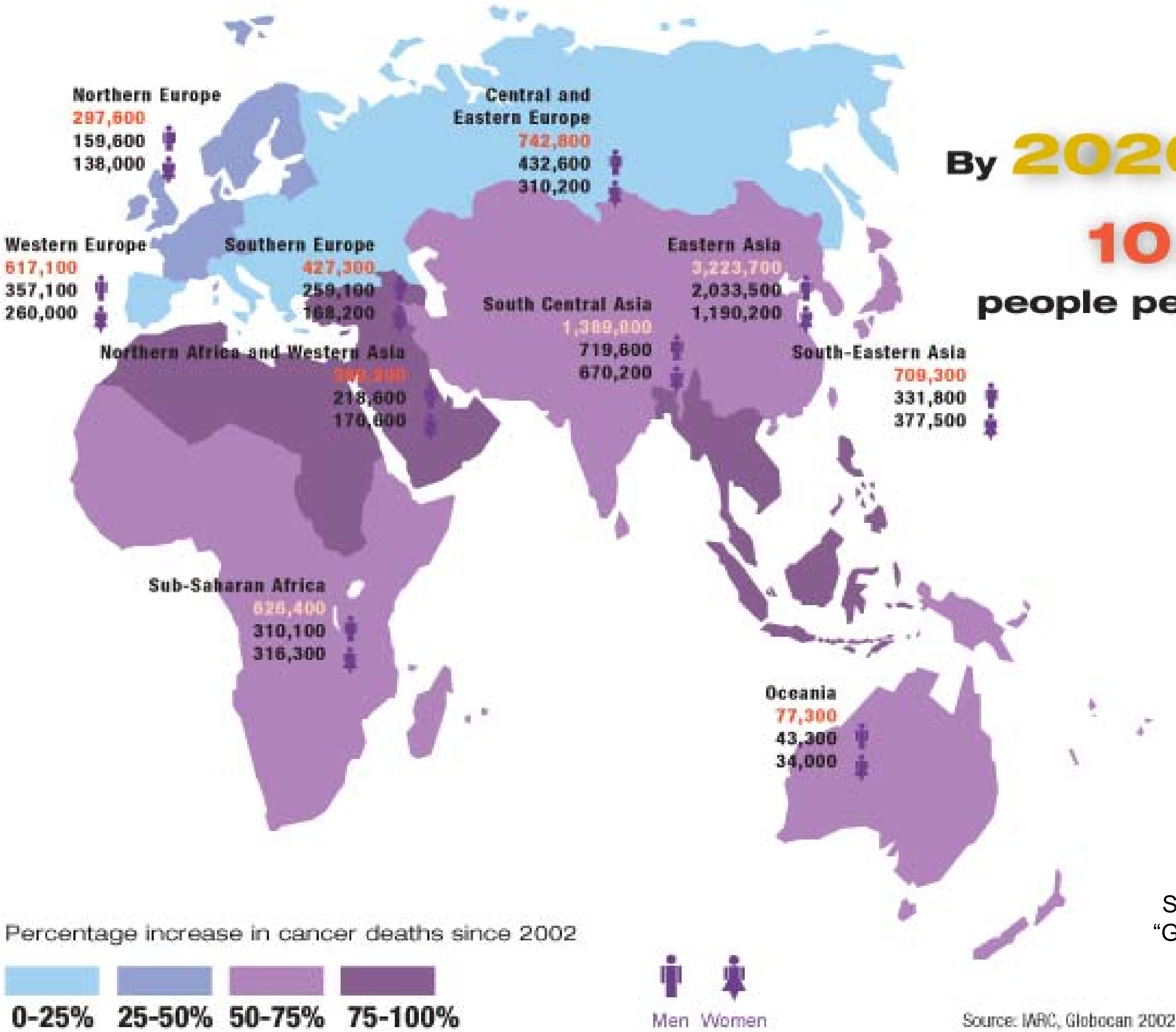
- ~ 560,000 Americans will die of cancer this year
- ~ 1.4 million Americans will be diagnosed with cancer this year
- ~ $213 billion for cancer healthcare costs
- Numbers of new cancer cases will increase by 30-50% as we approach 2020 (Aging of baby boomers, demographic shifts)



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.

And a Looming Global Healthcare Crisis

NCI Alliance for Nanotechnology

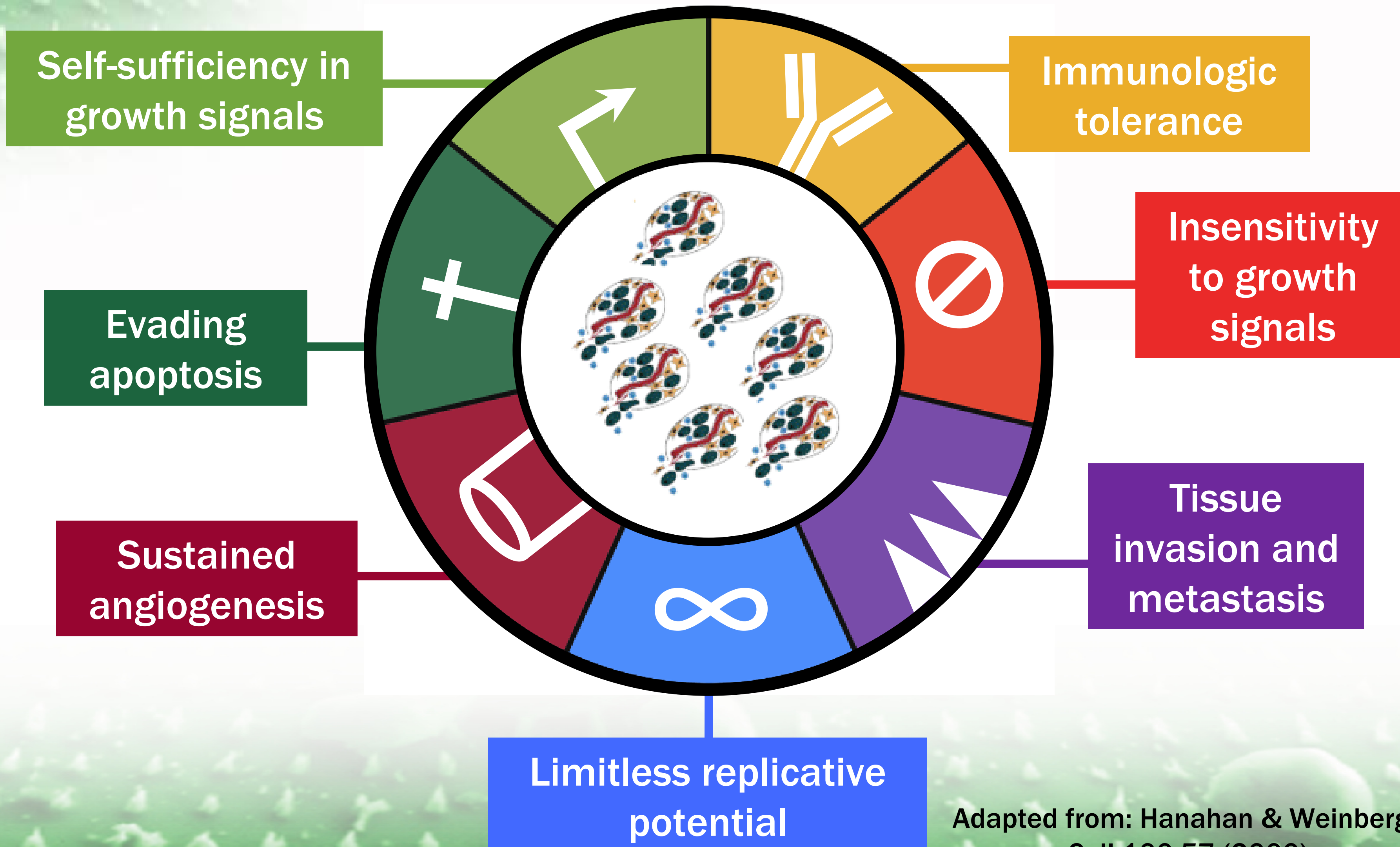


By 2020, cancer could kill 10.3 million people per year unless we act

Source: World Health Organization
"Global Action Against Cancer" 2005

The Daunting Complexity of Cancer at Every Level is a Major Barrier

NCI Alliance for Nanotechnology in Cancer



Adapted from: Hanahan & Weinberg, Cell 100:57 (2000)

Tumors are Heterogeneity – A Major Barrier

NCI Alliance for Nanotechnology in Cancer

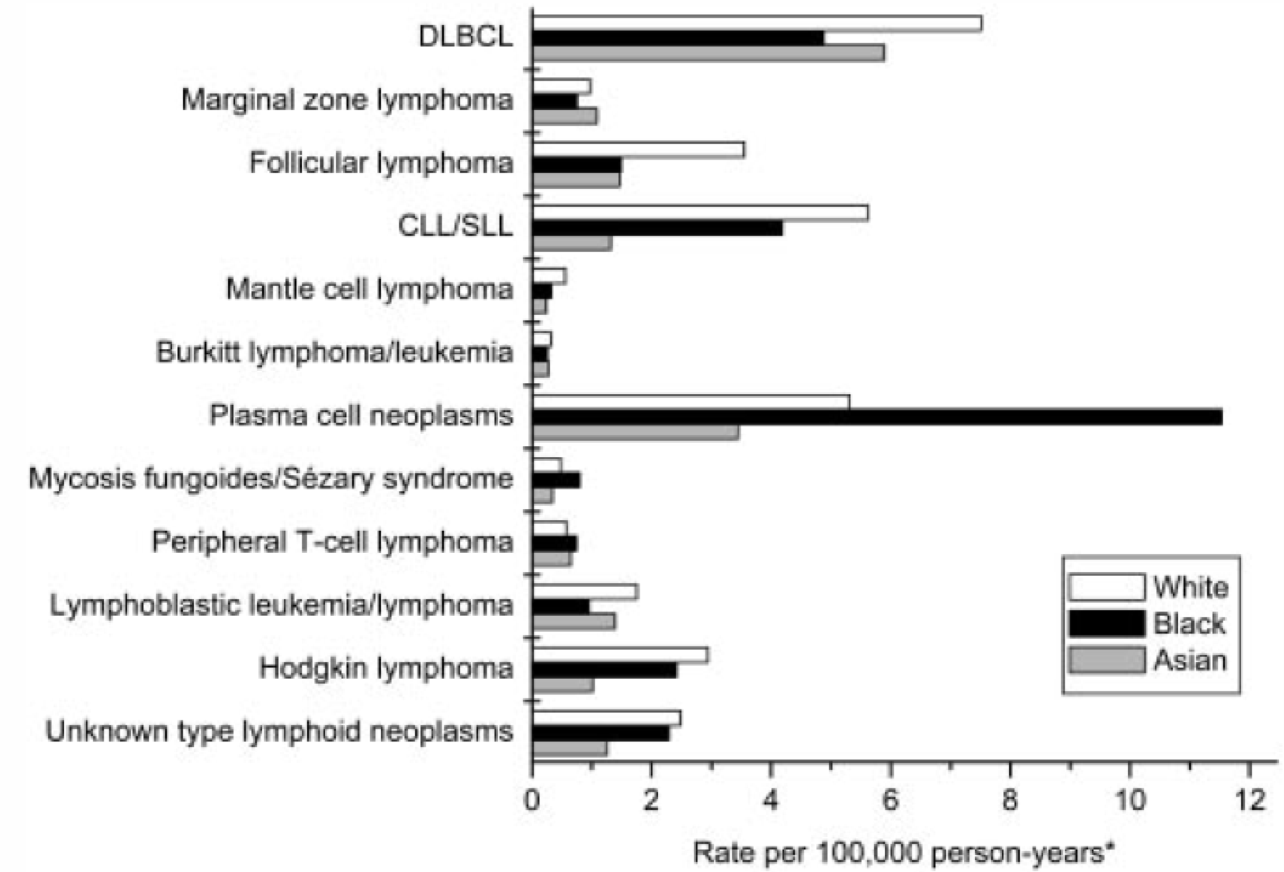


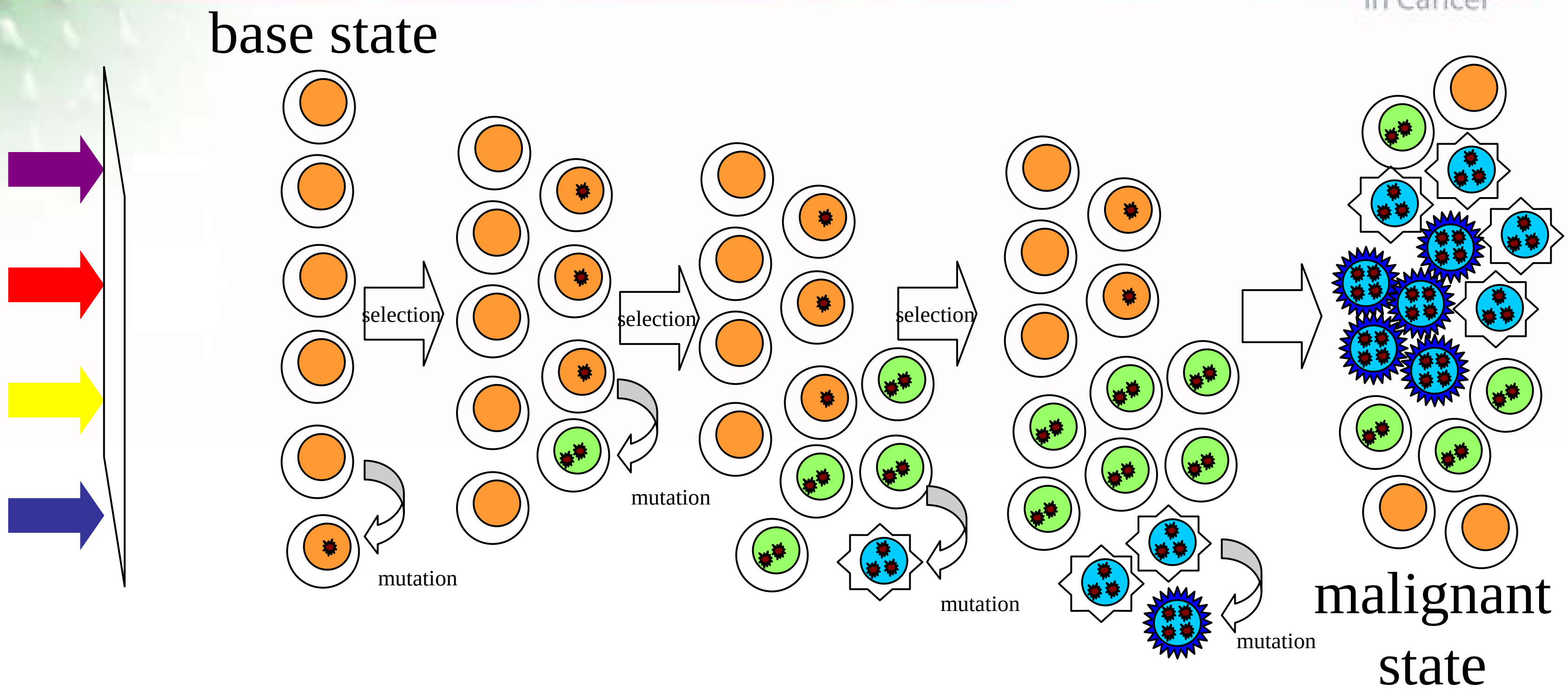
Figure 3. Incidence of lymphoid neoplasms by subtype and race, 12 SEER registries, 1992-2001. *All incidence rates are age adjusted to the 2000 United States population. Abbreviations are explained in Table 1.

Morton et al, Blood 2006

Cancer is a Complex Evolving System – Major Barrier

NCI Alliance for Nanotechnology in Cancer

- chemical
- virus
- hormone
- nutrition



We have Insufficient Knowledge of the "Biological Space" over time!

What will personalized approaches to cancer intervention require?

Cancer: Requires Capabilities to Interrogate Complexity – Nanotechnology Offers Unparalleled Possibilities

NCI Alliance for Nanotechnology in Cancer

Sub-Molecular

Genome

Transcriptome

Proteome

Epigenome

Spatial/Micro-environments

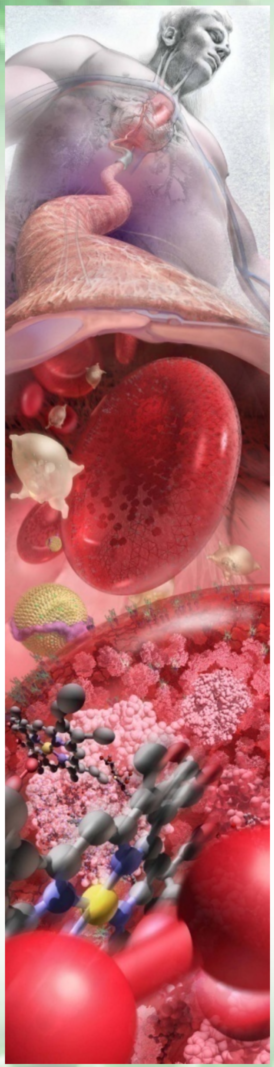
Complex Systems

Increasing layers of complexity (Ability to detect, transcribe, Interpret and report information)

Decreasing / limiting power of current Technologies (Promise of Nanotechnology)

Nanotechnology Offers Capabilities to Understand and Control Cancer Across Length Scales

NCI Alliance for **Nanotechnology** in Cancer



Length Scales	Players		Emergent 'Objects'
10^{-0} m	Organisms	→	Population
10^{-2} m	Organs	→	Organism
10^{-4} m	Cells	→	Organ
10^{-6} m	Organelles	→	Cell
10^{-8} m	Molecules	→	Organelle

Interactions

For decades biologists have been trying to understand complicated Biological systems of disease by understanding each part at its most basic level. However, we now look at how the interactions of all the 'players' (within a length-scale) lead to emergent 'objects'-properties that work together in complex tasks.

Cancer – A Disease of the Genes

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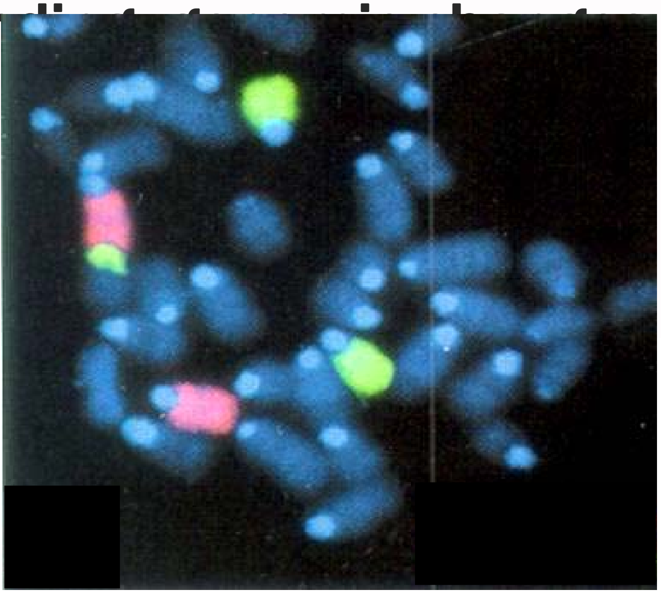
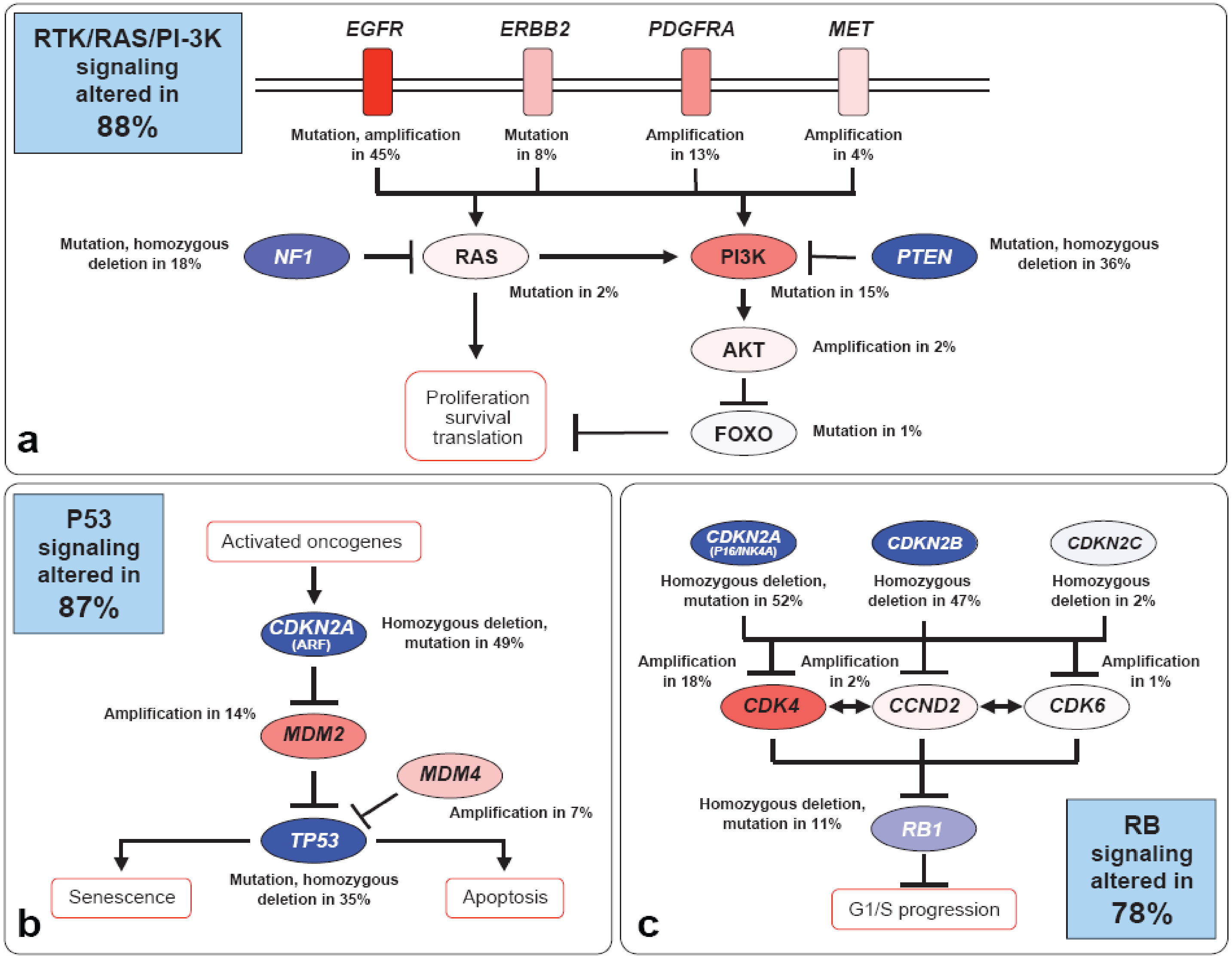
- **Biological significance of understan**
  in cancer:
  - **Copy number**
  - **Expression (regulation of)**
  - **Regulation of translation**
  - **Mutations**
  - **Epigenome**



Cancer is a disease of genomic alterations – identification of all genomic changes would enable defining cancer subtypes – potential to transform cancer drug discovery, diagnostics and prevention

Knowledge Expansion Challenges: The Cancer Genome Atlas (TCGA) – Glioblastoma Multiforme Mutations Assigned to Pathways

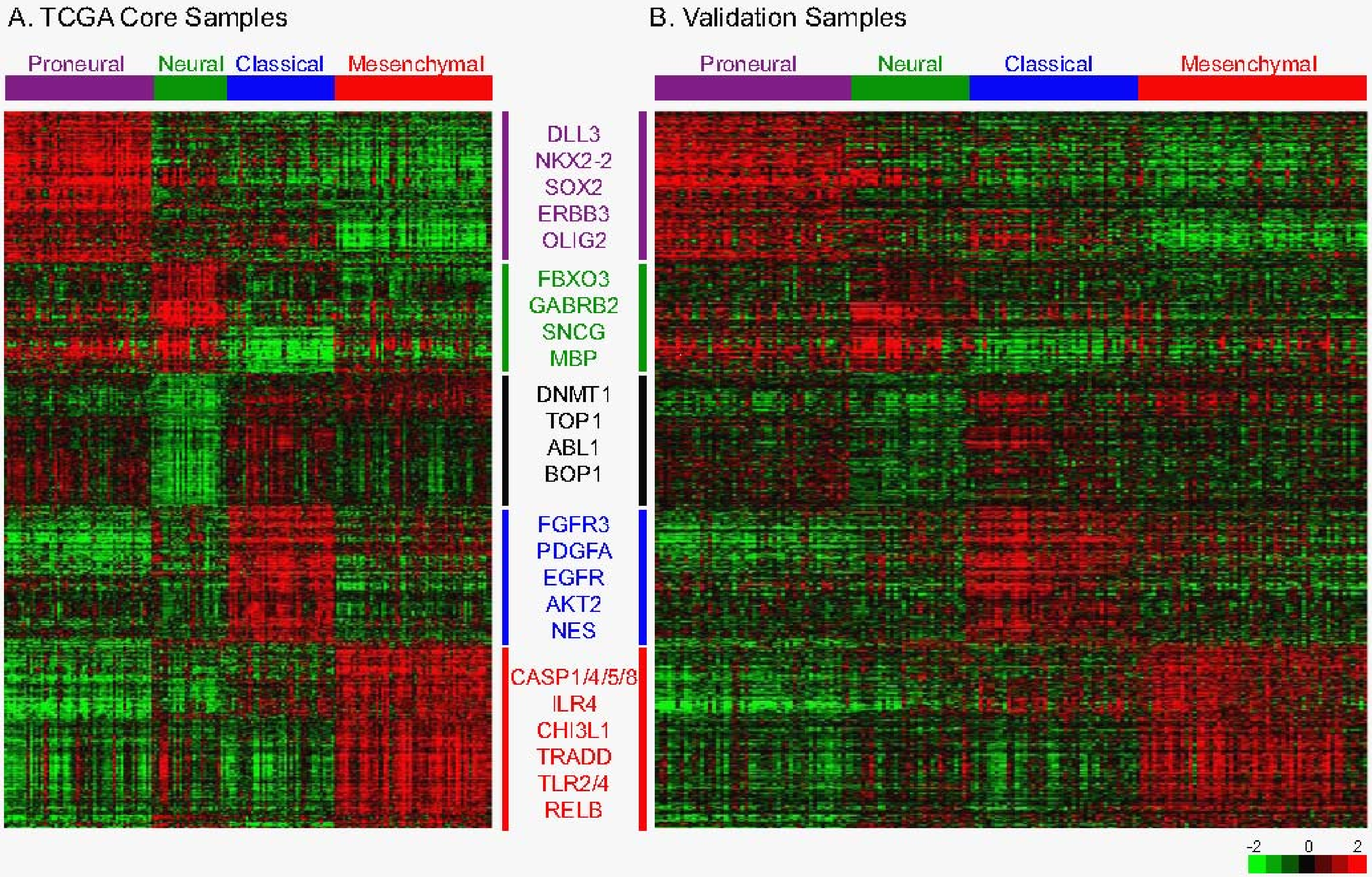
NCI Alliance for Nanotechnology in Cancer



TCGA: *Nature* 2008

Harnessing New Knowledge - Four Subtypes of GBM Were Identified

NCI Alliance for



Verhaak et al., submitted

The Major Barriers – Where Nanotechnology can Provide New Insights and Capabilities

NCI Alliance for Nanotechnology in Cancer

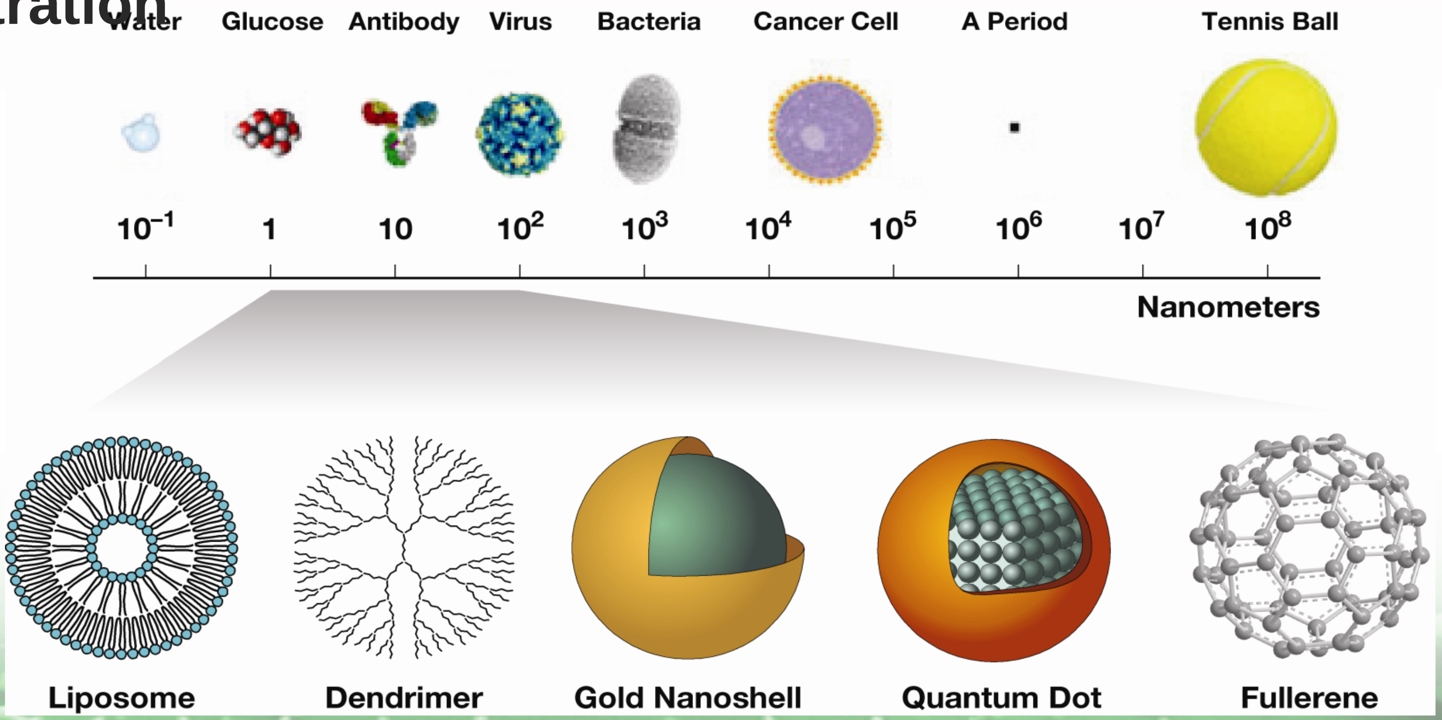
- Knowing all of the relevant information that drives cancer initiation and progression – understanding the biological space
- Defining the types and subtypes of cancer
- Capturing enough information to diagnose cancer at the earliest possible time
- Stopping cancer metastasis
- For established disease – defining what a therapeutic target is - and directing an agent to that target – sparing normal cells
- Combining cancer biomarkers that can diagnose cancer - with therapies to reach the specific molecular lesions identified by the diagnostic
- Monitoring the effectiveness of an intervention to identify resistance and address it
- Being unable to monitor the state of cellular/tissue homeostasis – sense specific pre-neoplastic changes (genomic, physical, etc.)

Why Nanotechnology for cancer diagnosis, treatment and prevention?

Nanotechnology: A Disruptive Technology with the Capability to Change the Development and Delivery of Cancer Interventions

NCI Alliance for Nanotechnology in Cancer

Varying dimensions and constructs lead to wide array of functional elements – classic physics meets quantum mechanics: increased surface to volume ratio; multiplexing capabilities; cell level access; targeted delivery; sustained/slow release and residence; enhanced tissue penetration



Nanotechnology and the Future of Cancer Interventions

NCI Alliance for
Nanotechnology
in Cancer

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

- **Early detection –** **highly sensitive and specific sensors**
- **In-vivo imaging –** **new contrast agents, localization**
- **Therapeutics –** **local, on-particle delivery**

Nanotechnology Offers Opportunities for Unprecedented Levels of Sensitivity for High Content Diagnostics

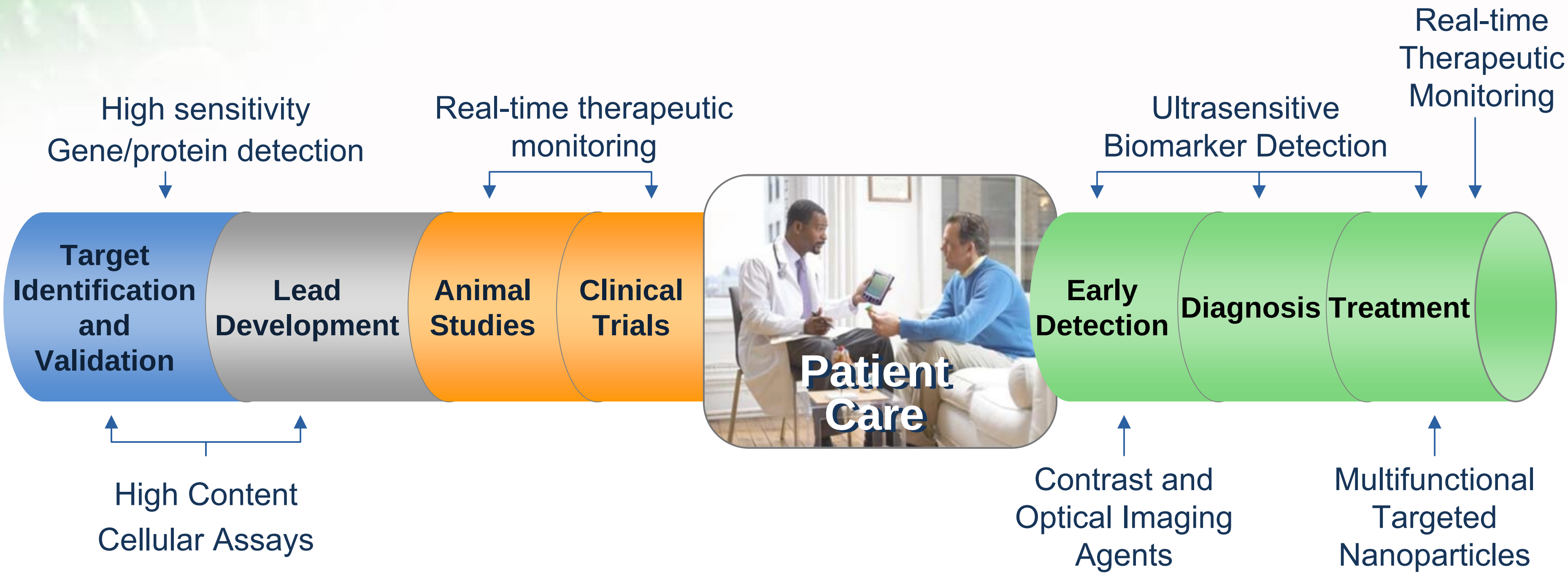
NCI Alliance for
Nanotechnology
in Cancer

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 Technologies Cancer: Prostate, Ovarian, Breast Alzheimer's Disease, Mad Cow Pulmonary Disease, Cardiovascular Disease
10^{-18}- Attomolar	Tens	
10^{-21}- Zeptomolar	<1	

Nanotechnology Holds Significant Promise for Cancer Detection, Treatment, Prevention:

NCI Alliance for Nanotechnology in Cancer



NCI's Nanotechnology Alliance for Cancer

Alliance for Nanotechnology in Cancer (ANC): Multidisciplinary and Milestone-driven

- NCI's long history in nanotechnology – dates back to the Unconventional Innovation program preceded the Alliance
- Planning for the ANC began in early 2003
- ANC Launched in September 2004
- Milestone driven – and focused on team science
- Included a network of centers (CCNEs), novel platforms, training programs and the Nanotechnology Characterization Laboratory
- Critical infrastructure support to facilitates clinical translation of discoveries through Nanotechnology Characterization Laboratory – focus on health and safety issues
- Multiple interagency collaborations- NIST, FDA, etc.
- Major focus on translational science and technology commercialization

Major Programs of the Alliance

NCI Alliance for Nanotechnology in Cancer

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**

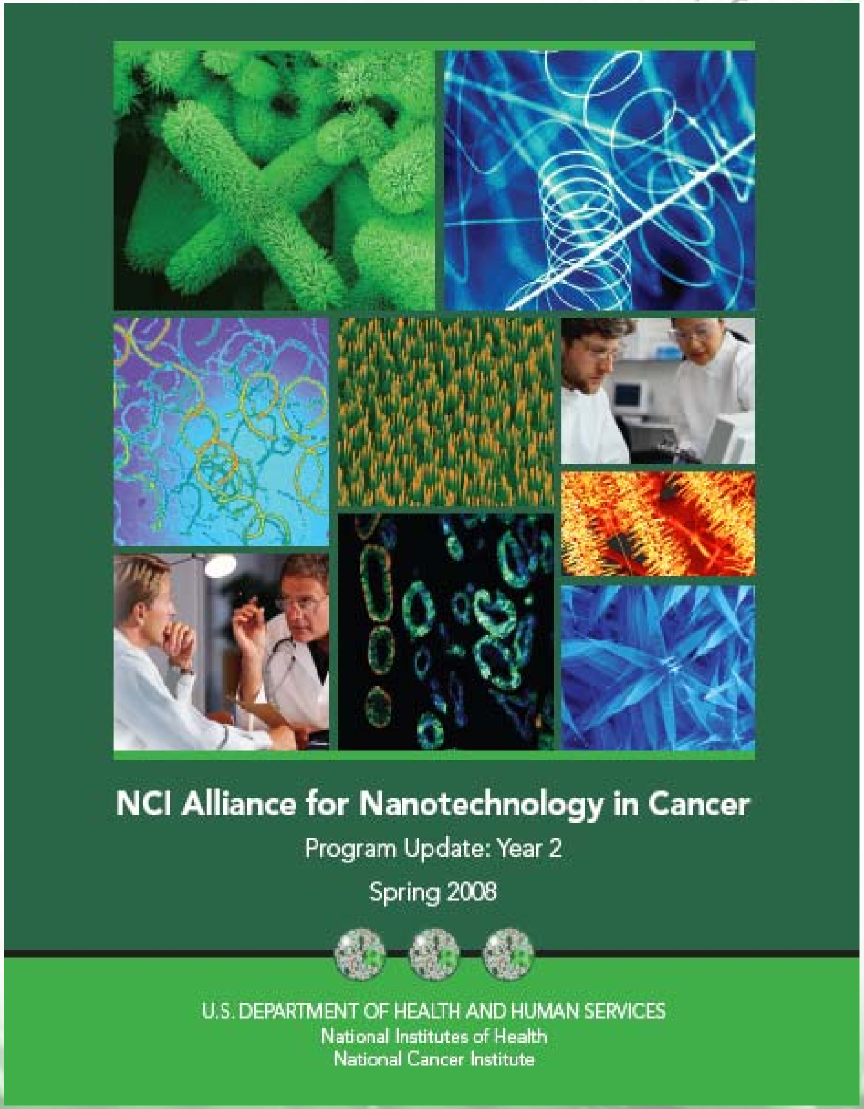
Inaugural Years for the NCI's Alliance for Nanotechnology in Cancer

NCI Alliance for Nanotechnology

Established in 2004 – Renewed for 5 years

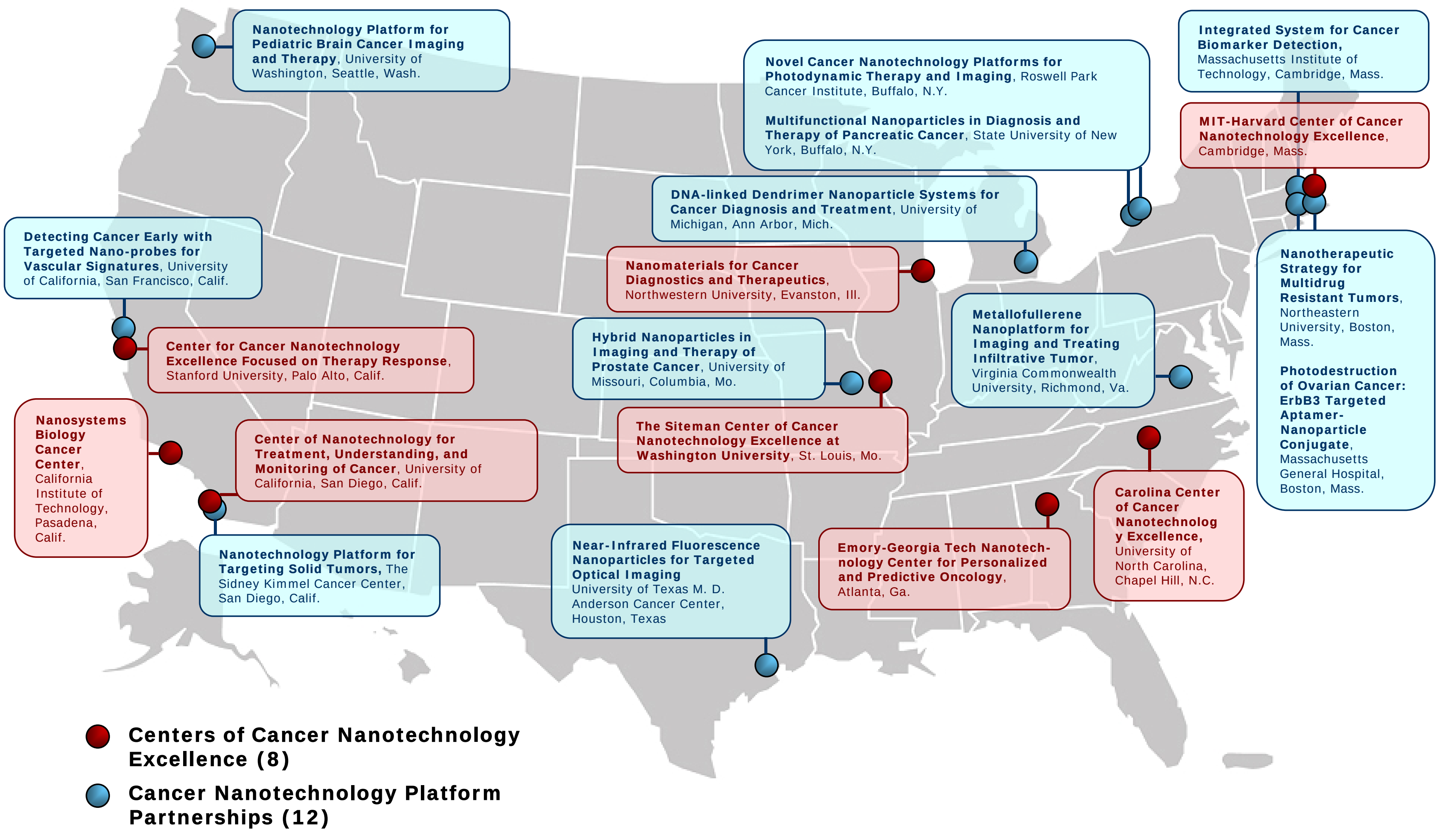
- **Scientific output :** Over 1000 peer-reviewed journal papers published with average impact factor ~7. Strong evidence of establishing joint projects: growing number of publications involving multiple PIs
- **Clinical Translation:** 8-10 clinical trials underway; several companies in pre-IND discussions with FDA
- **Commercialization Efforts:** over 50 companies associated with the Alliance – 10 formed in last year
- **Technology:** Over 200 disclosures and patents filed
- **NCL**: Leader in characterization of nanotechnologies
- **Leveraged funding:** Significant additional funding to CCNEs (grants, philanthropy, industry, and venture investors.

Unprecedented Teams, Technology - Science Convergence and - Engagement of Cancer Biologists and Oncologists



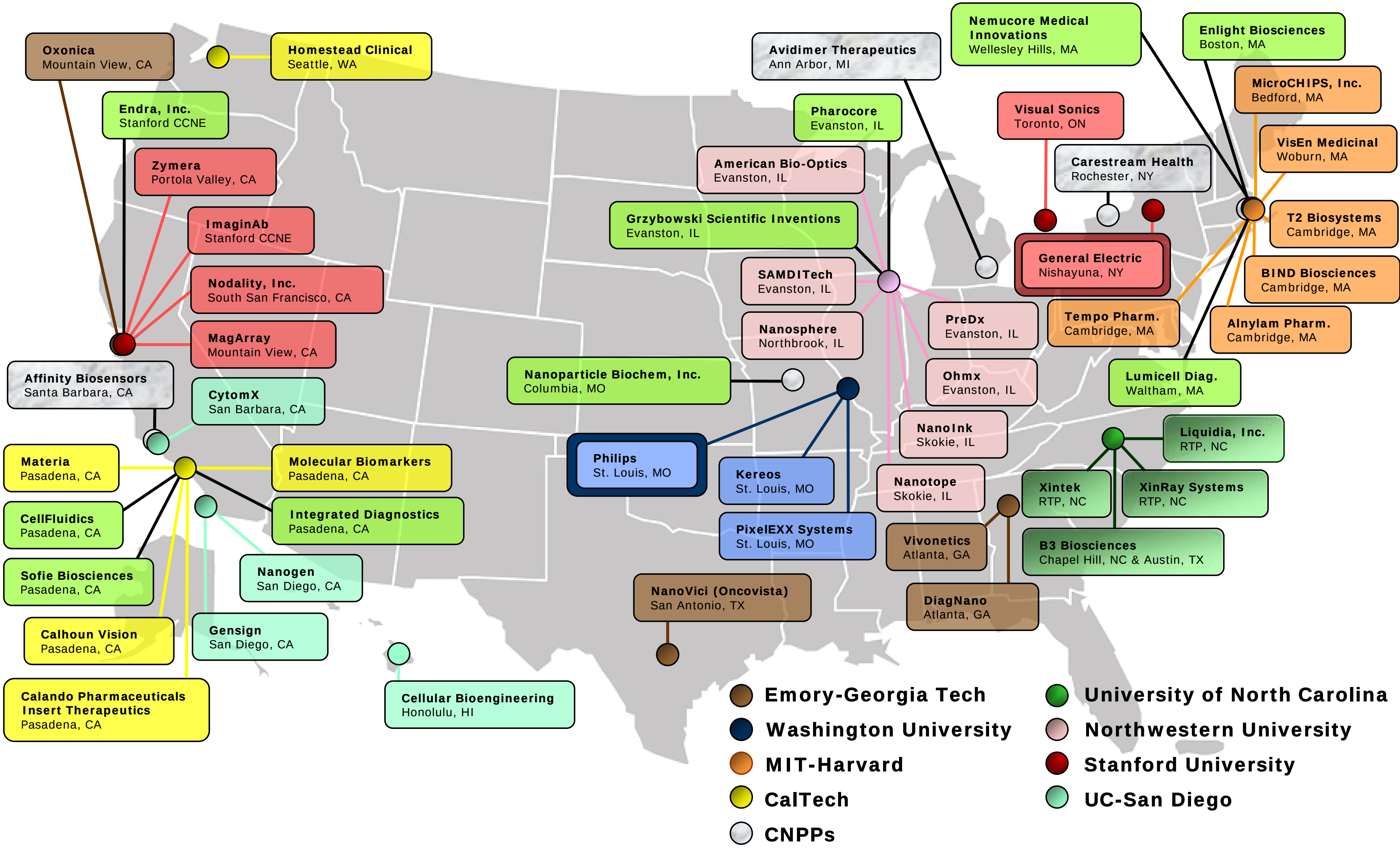
NCI's Alliance for Nanotechnology in Cancer (Centers and Platforms)

NCI Alliance for Nanotechnology



NCI Nanotechnology Alliance and Commercial Partners

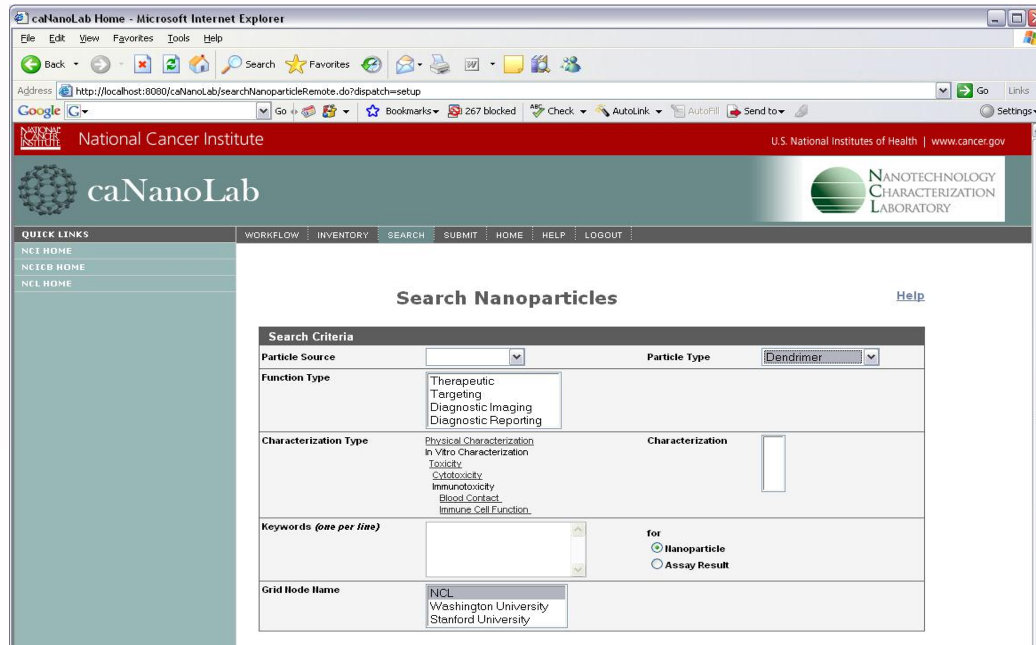
NCI Alliance for Nanotechnology

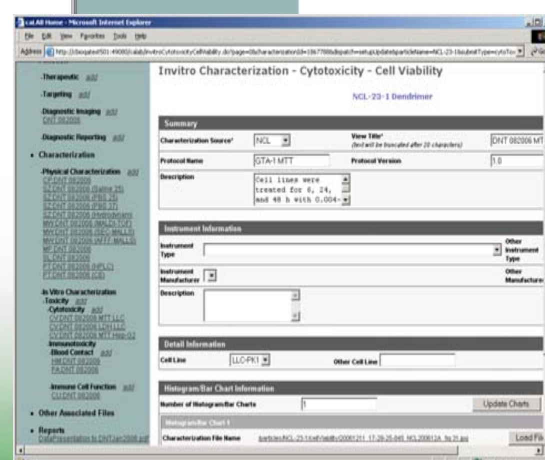


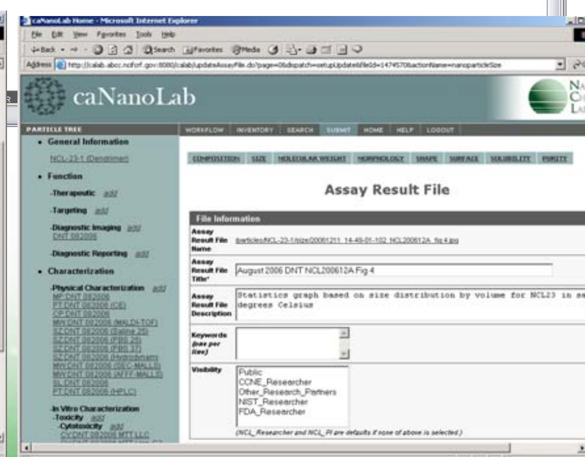
Common Data Storage- caNanoLab Database

NCI Alliance for Nanotechnology in Cancer

- Standards Development.
  - Terminology
  - Ontologies
- Searchable database
  - Particle data
  - In vitro data
  - In vivo data
- Role-based security
  - NCL view
  - Alliance view
  - Public view
- Interface with caBIG



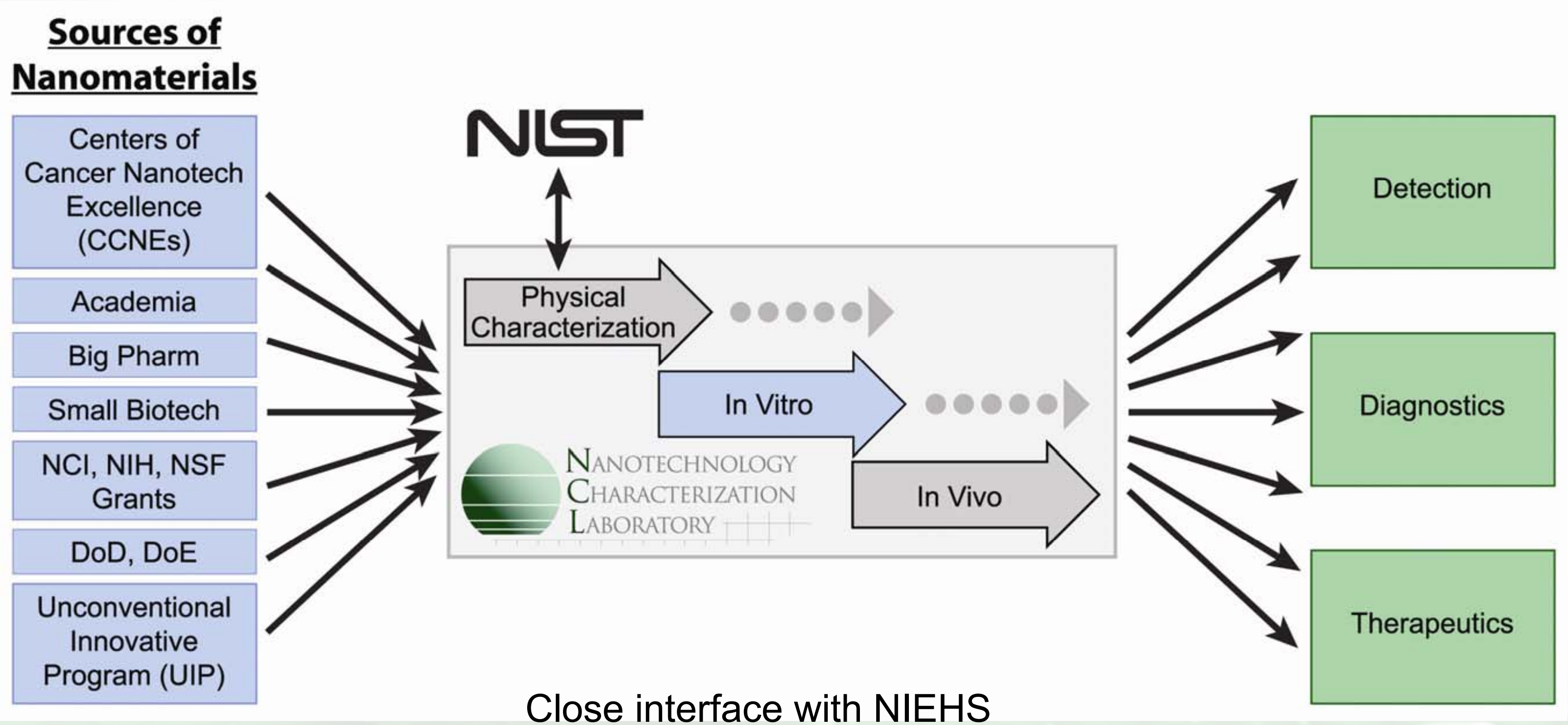




NCI Nanotechnology Characterization Laboratory (NCL) - Proactively Addressing Health and Safety Questions

NCI Alliance for Nanotechnology in Cancer

- **standardization of materials characterization**
- **acceleration of clinical translation**

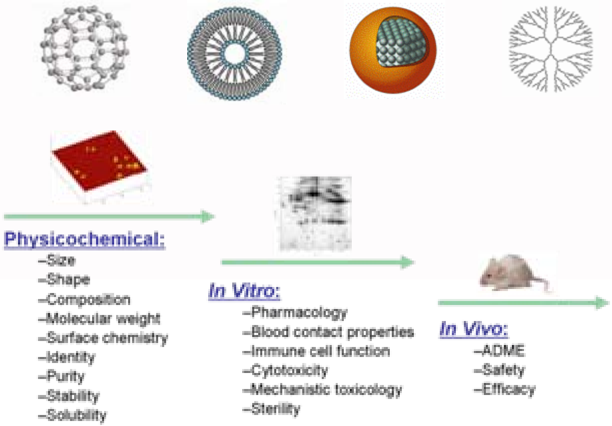


NCL is a formal collaboration between NCI, FDA and NIST

Nanotechnology Characterization Laboratory (NCL)

NCI Alliance for
Nanotechnology
in Cancer

- Interagency collaboration with FDA and NIST to develop and standardize characterization methodology for nanomaterials
- NCL achieved prominent standing in nanotechnology community and is used as a model for establishing efforts in academia and industry
- Serving as a bridge to bring NCI and Alliance nanotech investigators to the FDA



Achievement:

- More than 165 individual nanoparticles undergoing characteriza
  - 50 Active collaborations (MTAs)
  - In 2008, 14 new MTAs, 13 CDAs, 1 CRADA with GE
  - 45 animal studies to date

Scott McNeil
Anil Patri

Timeline: Moving into second phase of Cancer Nanotechnology

NCI Alliance for Nanotechnology in Cancer

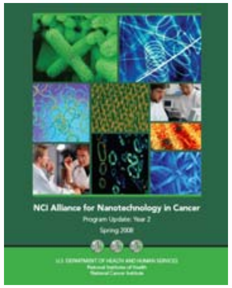
Cancer Nanotechnology Plan Published

NANOTECHNOLOGY CHARACTERIZATION LABORATORY

NCL Launches

NCI Alliance for Nanotechnology in Cancer

Phase I Awarded



Evaluation and Update

- **Scientific Output**
  - Over 1000 pubs
- **Clinical Translation**
  - 50 companies
  - Over 200 patents
  - 8-10 clinical trials

NCI Alliance for Nanotechnology in Cancer

Program Renewed

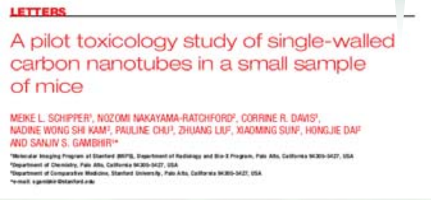
RFA Released

NCI Alliance for Nanotechnology in Cancer

Phase II Clinical Focused

2004 **2005** **2006** **2007** **2008** **2009** **2010**

Nano Imaging



LETTERS

A pilot toxicology study of single-walled carbon nanotubes in a small sample of mice

MEIKE L. SCHIPPER, NOZOMI NAKAYAMA-RATCHFORD, CORRINE R. DAVIS, NADINE WONG SHI KAM, PAULINE CHU, ZHUANG LIU, XIAOMING SUN, HONGJIE DAI AND SANJIV S. GAMBHIR

Nano Diagnostics

Vol 464 | 15 April 2010 | doi:10.1038/nature08956 nature

LETTERS

Evidence of RNAi in humans from systemically administered siRNA via targeted nanoparticles

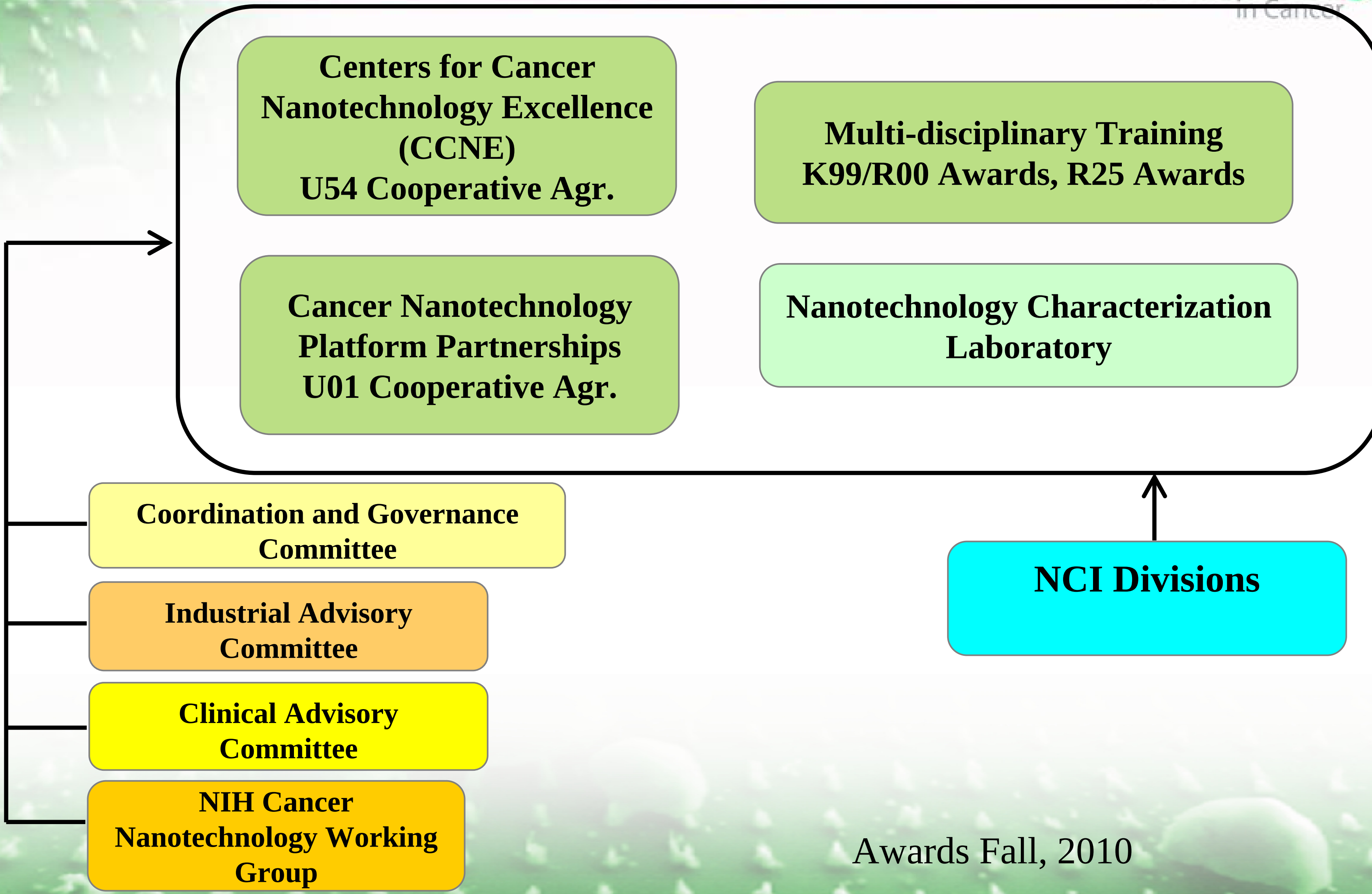
Mark E. Davis, Jonathan E. Zuckerman, Chung Hang J. Choi, David Seligson, Anthony Tolcher, Christopher A. Alabi, Yun Yen, Jeremy D. Heidel & Antoni Ribas

Nano Therapy

Basic **Translational** **Pre-Clinical** **Clinical**

NCI Alliance for Nanotechnology in Cancer – Open Competition Phase II (Organizational Structure)

NCI Alliance for Nanotechnology in Cancer



Awards Fall, 2010

http://nano.cancer.gov

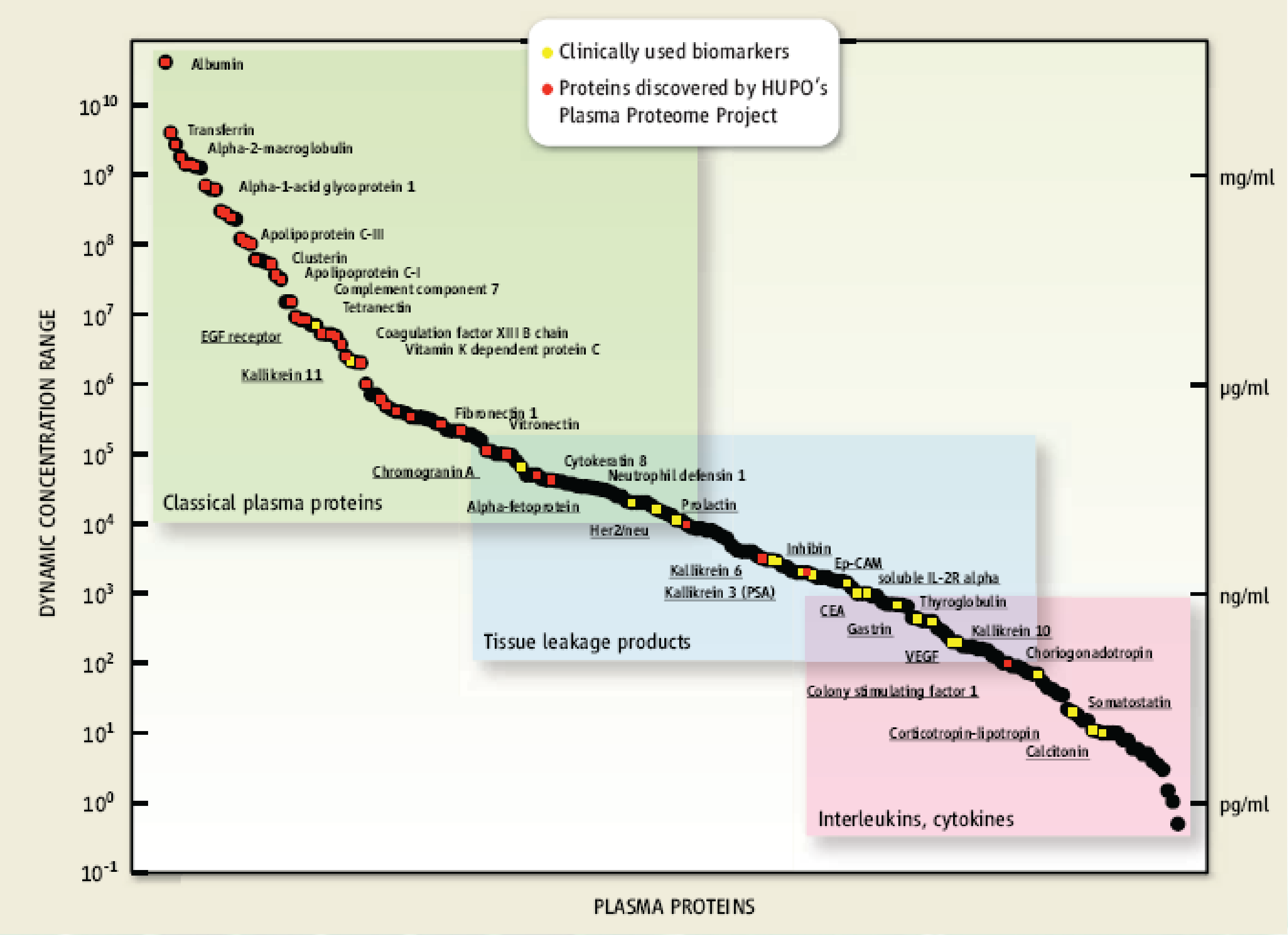
NCI Alliance for Nanotechnology in Cancer

- Timely reports of scientific advances
- Accessible, searchable updates on advances and scientific bibliography
- Teaming site for potential collaborations
- Multimedia communications
- Sign-up for email alerts

The Future: Science from the Alliance

Meeting Diagnostics Challenges Through Nanotechnology - High Content Assays for Proteins

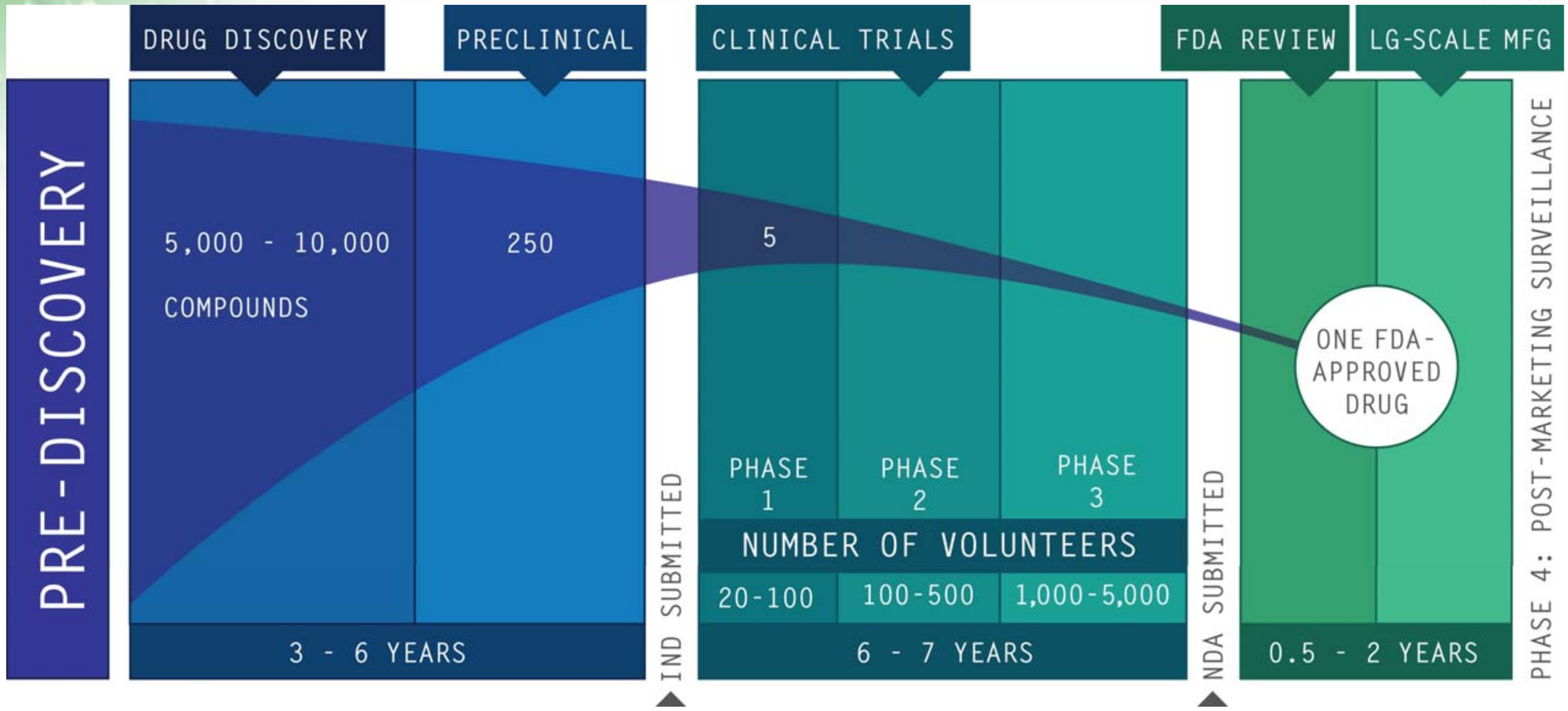
NCI Alliance for Nanotechnology in Cancer



Science, 2008

Nanotechnologies are Addressing Toxicity - Delivery – Efficacy Barriers in Drug Development

NCI Alliance for Nanotechnology in Cancer

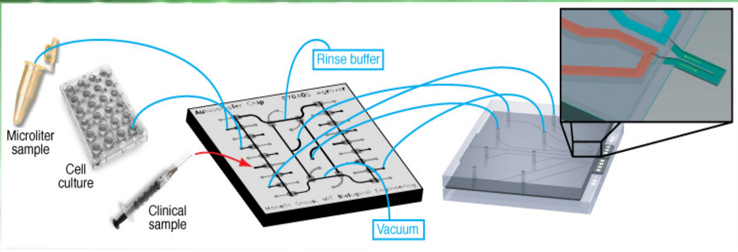


Time and attrition are both directly related to **insufficient knowledge of biological space**

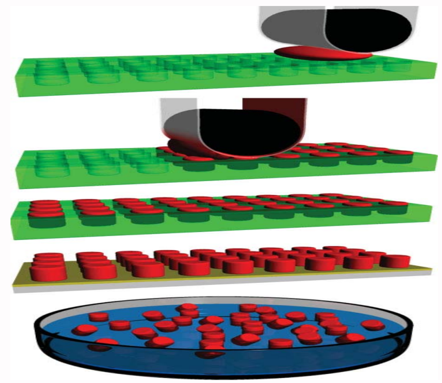
~ US$ 1 Billion

The NCI's Nanotechnology Alliance – Examples of Paradigm Shifting Approaches to Cancer Diagnosis and Treatment

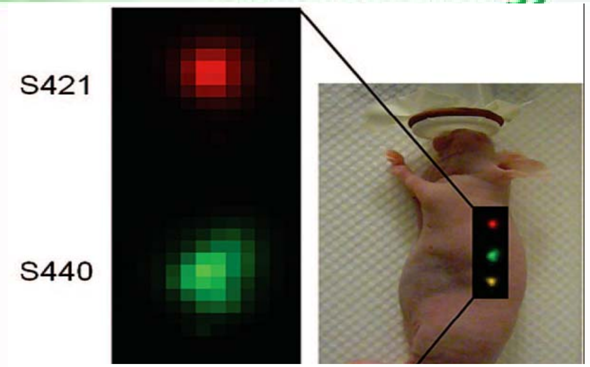
NCI Alliance for
Nanotechnology



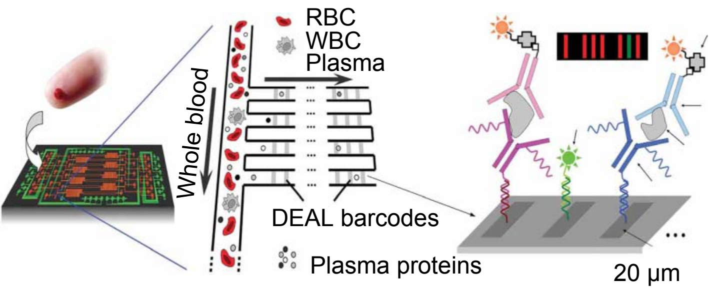
Scott Manalis, MIT CNPP
- Ultra-sensitive detection of circulating tumor cells using suspended microchannel resonant mass sensor (SMR) has been demonstrated.
- Electrokinetic concentrator (1 million fold) allows for evaluating samples of very low concentration (1 fg).



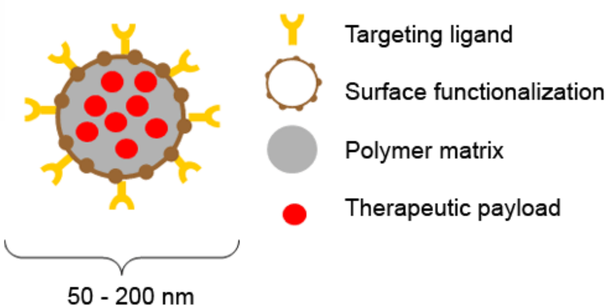
Joe DeSimone, UNC CCNE
- Diversified nanoparticle fabrication platform has been developed based on semiconductor lithographic techniques. Accurate control of particle size, shape, and cargo can be achieved.



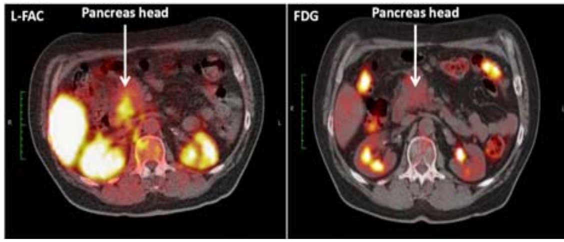
Sam Gambhir, Stanford CCNE
- Gold nanoparticles and carbon nanotubes have been used as surface-enhanced Raman labels for multiplexed *in vivo* imaging of tumors in Raman spectroscopy. This technique allows for rapid studies of the effects of nanoparticle size, targeting, and drug dosing affects.



Jim Heath, Caltech/UCLA CCNE
Integrated Blood Barcode Chip
- Multiplexed protein detection from whole blood
- Microfluidic whole blood separation
- DNA Encoded Antibody Library barcode assay
- Cancer marker detection
- Less than 10 minute working time



O. Farokhzad & R. Langer, MIT/Harvard CCNE
- Efficacy of paclitaxel and doxorubicin delivered using PSMA targeted PLGA nanoparticles has been demonstrated

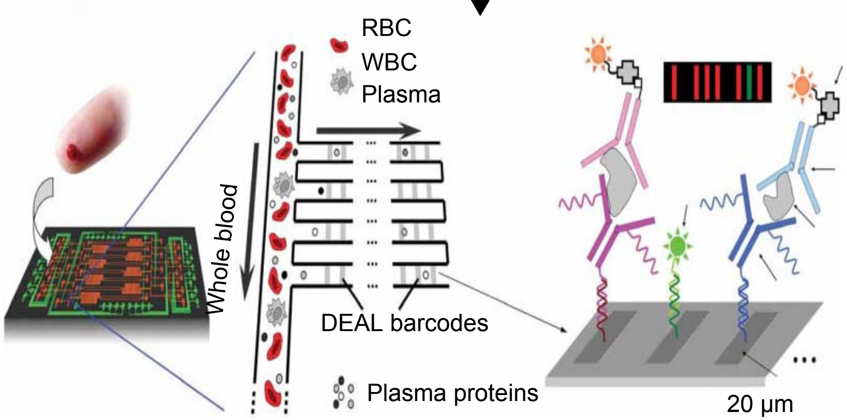


Michael Phelps, Caltech/UCLA CCNE
- [18F]FAC PET probe, synthesized in microfluidic circuits, is being evaluated for biodistribution in newly started clinical trial.

In vitro Diagnosis and Post-therapy Monitoring Using Large-scale, Multi-parameter Protein Analysis in Microfluidic Devices

NCI Alliance for Nanotechnology in Cancer

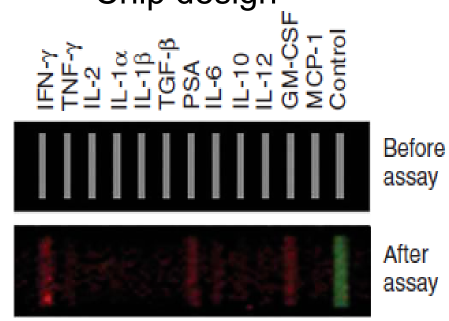
Integrated blood barcode chip (IBBC)
Plasma is separated from a finger prick of blood using multiple DNA-encoded antibody barcode (DEAL) arrays patterned within microfluidic plasma-skimming channels for multiplex fluorescence detection.



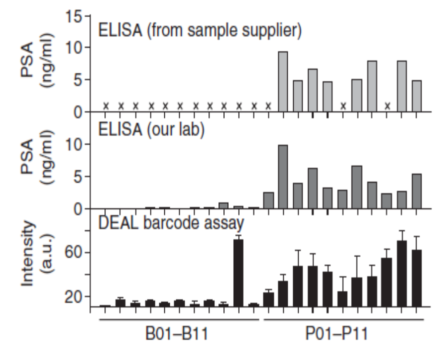
Multiplexed protein measurements of clinical patient sera for prostate and breast cancers. IBBC chip is used to measure the cancer marker PSA and 11 cytokines from 22 cancer patient serum samples. B01–B11, samples from breast cancer patients; P01–P11, samples from prostate cancer patients.

James Heath, Ph.D.
California Inst. of Technology

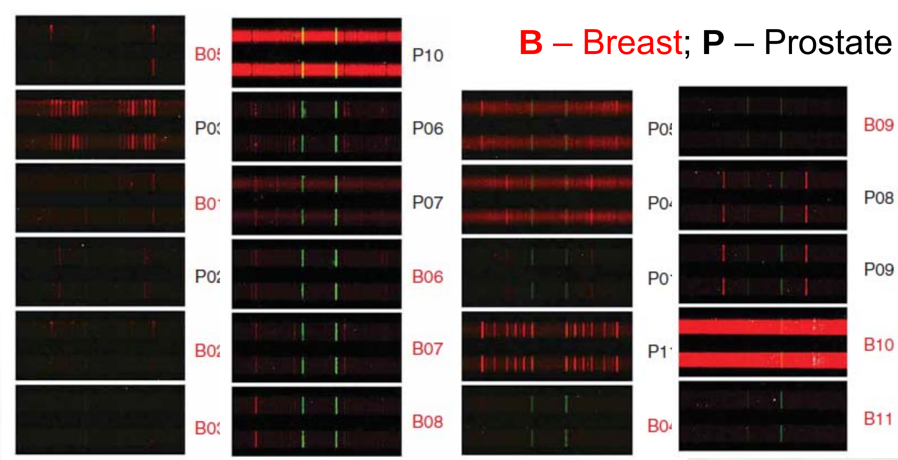
Chip design



ELISA validation of barcode assay



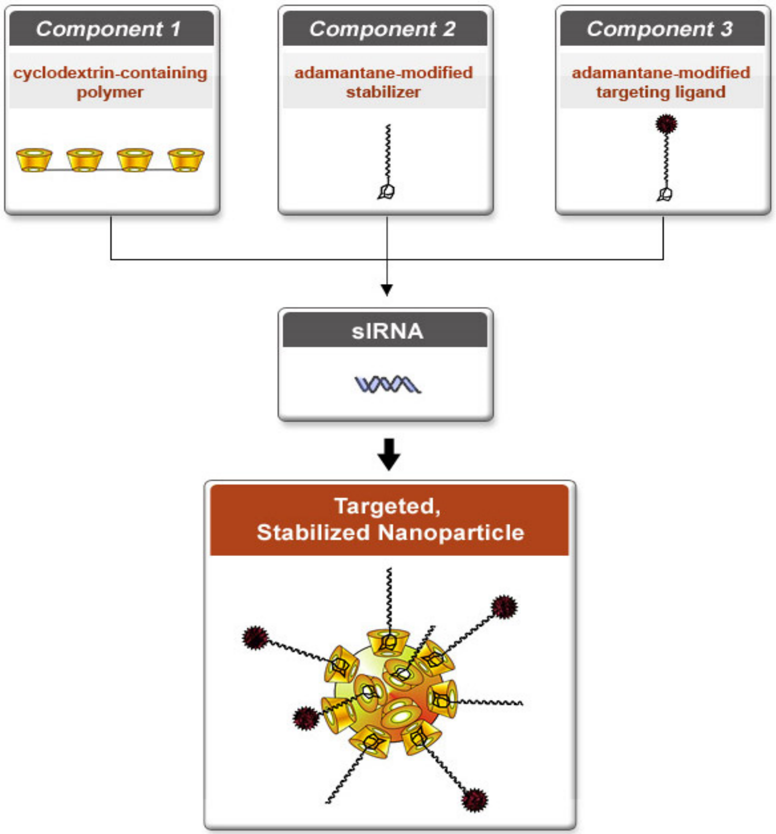
B – Breast; **P** – Prostate



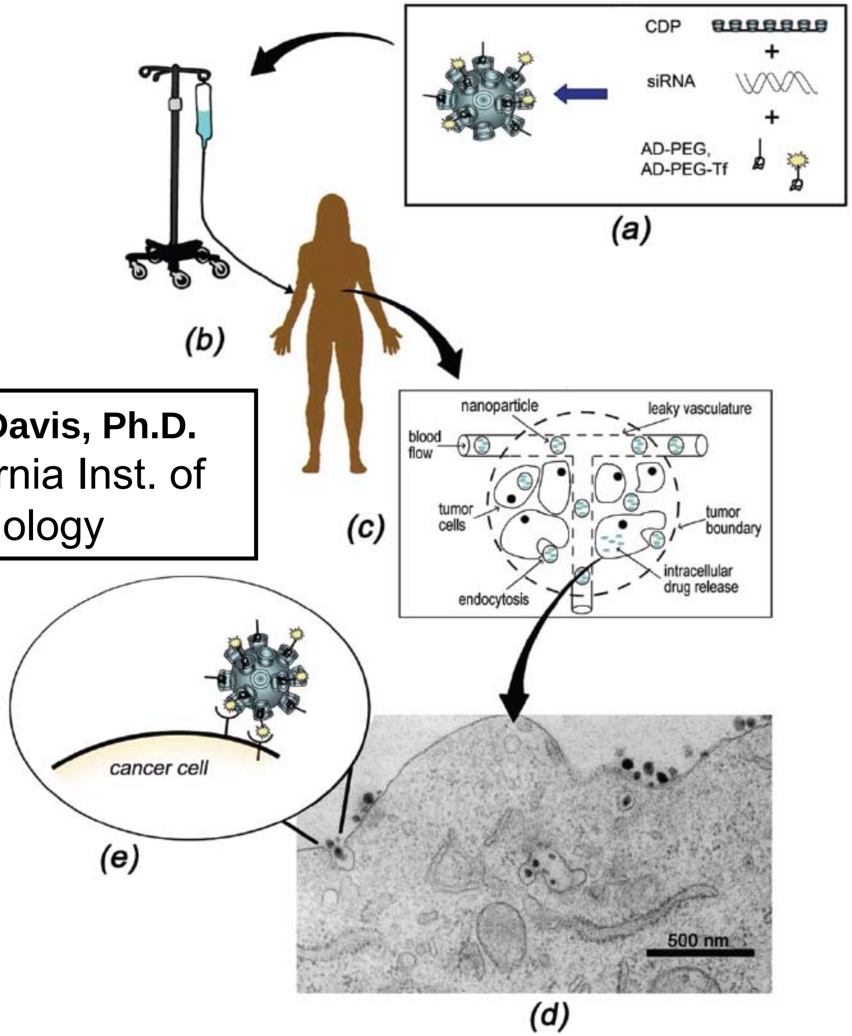
CHIP 1 CHIP 2

Lab Chip 9, 2016 (2009)
Nature Biotech 26, 1373 (2008)

First Targeted Delivery of siRNA Therapy Using Cyclodextrin Polymer Based Nanoparticles



Mark Davis, Ph.D.
California Inst. of Technology



Formulation of targeted nanoparticle-containing siRNA:
- Water-soluble, linear cyclodextrin-containing polymer
- Adamantane-PEG conjugate
- Targeting component (human transferrin)

Steps in the systemic delivery of siRNA to tumor cells:
- Nanoparticles are infused into patients
- Circulation in the blood
- Penetration through the tumor and endocytosis

FIRST FORMULATED, TARGETED, SYSTEMIC siRNA DELIVERY TO ENTER THE CLINIC (PHASE I for SOLID TUMORS)

Nature 464, 1067 (2010)

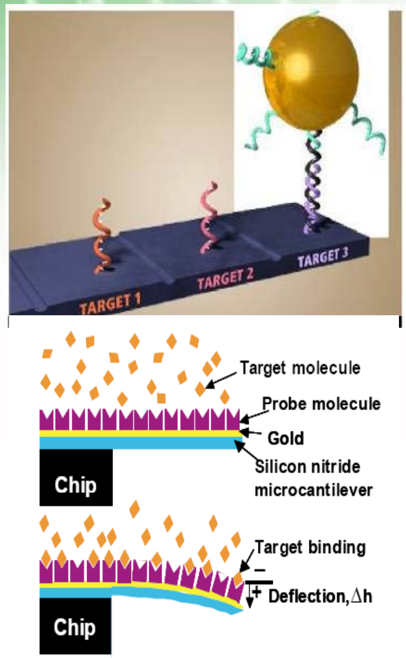
Examples of Early Stage Nano-Based Cancer Therapies and Imaging Agents

NCI Alliance for Nanotechnology in Cancer

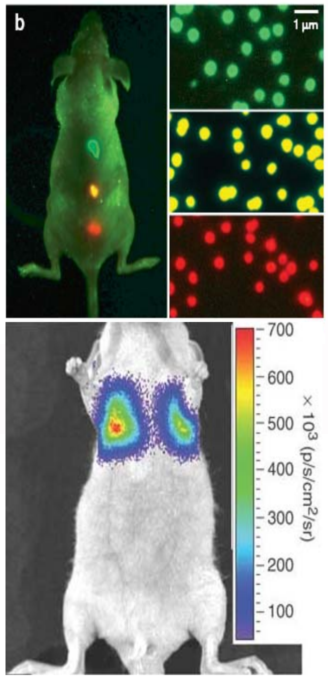
Company	Product(s)	Material	Indication	Status	Admin.
Advanced Magnetics	Combidex	Iron oxide nanoparticles	Tumor imaging	Conditional FDA approval	IV
Avidimer	Platform, ATI-001	Targeted dendrimers	Various cancers	Pre-clinical	IV
BIND	Platform technology	Targeted PLGA-PEG nanoparticles	Prostate cancer, others	Pre-clinical	IV
Carbon Nanotechnology	DF1	Dendritic fullerene	Chemoprotection	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
Kereos	Platform technology	Perfluorocarbon polymers	Cancer and cardiovascular	Starting Phase I	IV
Liquidia Technologies	Platform technology	PRINT™ nanoparticles	Cancer, others	Pre-clinical	IV
Triton Biosystems	TNT-Anti-Ep-CAM	Polymer-coated iron oxide	Solid tumors	Pre-clinical	IV

Nanotechnology is an Enabler of New Solutions for Cancer

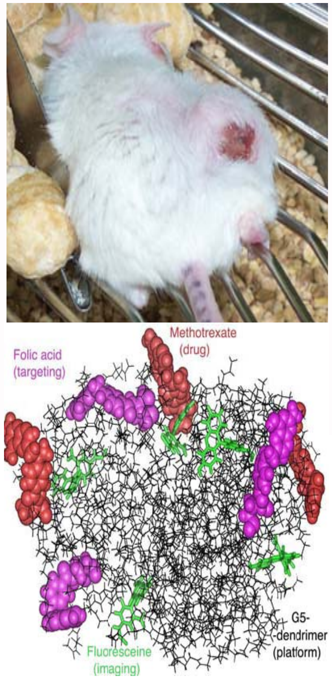
NCI Alliance for Nanotechnology in Cancer



Detection



Imaging



Therapy

- Multiple functions
  - Target, trace, treat
- In vitro sensing and in vivo imaging capabilities
  - Improved sensitivity
  - Multi-modal imaging
- Non-invasive treatment
  - Localized therapy
  - Lower dose used
  - Improved side effect profile

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

Challenges: As With Any New Widespread Technology

NCI Alliance for Nanotechnology in Cancer

- Concerns about safety
- Exaggerated expectations of timeline for impact
- Media coverage tends to extremes

Associated Press

Posted October 10, 2006

FDA Gets Mixed Advice On Nanotechnology

REUTERS

Posted October 11, 2006

FDA told to watch nanotech products for risks

Health News Daily

Posted October 11, 2006

FDA Short On Nanotechnology Expertise, U. Md. Professor Says

PR Newswire
United Business Media

Posted October 9. 2006

Nanotechnology: It's Knocking on FDA's Door

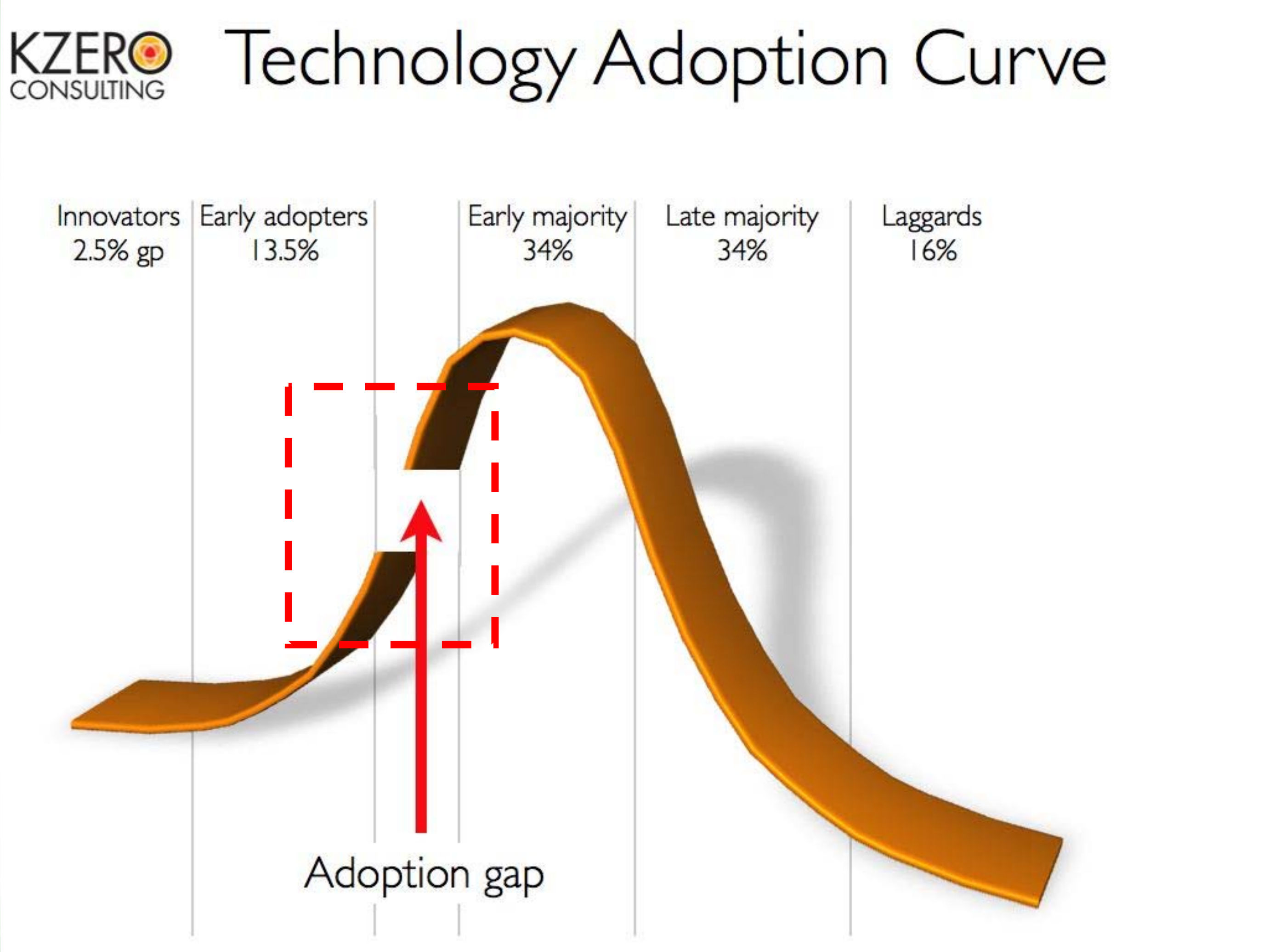
Associated Press

Posted October 11 , 2006

FDA eyes tiny particles

Major Challenge – Shift from Classic Small Molecule Therapies and Classic Immunoassays to Nanotechnologies

NCI Alliance for
Nanotechnology
in Cancer



Why Nanotechnology for Personalized Cancer Medicine?

NCI Alliance for Nanotechnology in Cancer

- Cancer can generally be successfully treated – if diagnosed early – Key efforts are already underway using multiple nanotechnologies to increase sensitivity of high information content assays
- Cancer is an exceedingly complex disease (potentially hundreds of genomic changes – possibly thousands of proteomic changes to measure for diagnosis) – Platforms are leveraging the fact that nanotechnology is not numbers/parameters limited
- Specific delivery to the target is critical for cancer – now and in the future – power of delivering therapies via nanotechnologies is well demonstrated
- Imaging offers enormous potential for both diagnosis and therapy – especially functional imaging – improvements in imaging (nearly all types) are increasingly driven by nanotechnology approaches
- Multiplexing functions is necessary for cancer detection and treatment (need to detect – deliver – report – monitor – re-deliver) – Multiplexing platforms are constantly improving – moving into clinical trials
- Sensing changes in tissues/microenvironments could enable preventive strategies – biosensors are in development – realistic possibilities