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
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

## Advances in Molecular Research and Technologies

<table>
<thead>
<tr>
<th>The Past Century</th>
<th>21st Century</th>
</tr>
</thead>
<tbody>
<tr>
<td>Established system to treat established disease – a treatment/therapeutic focus (in cancer often too late)</td>
<td>Shift to targeted Interventions for prevention and treatment – shift in focus to early detection and prevention</td>
</tr>
<tr>
<td>Morphologic and pathologic diagnosis – drove treatment</td>
<td>Driven by the molecular characterization of disease – mechanistic understanding of pathways and processes</td>
</tr>
<tr>
<td>Expensive in all respects – not sustainable in 21st century</td>
<td>Evidence based – preserves human and financial capital – sustainable – Health becomes major national asset</td>
</tr>
<tr>
<td>Healthy population not a focus as a major national advantage/asset</td>
<td></td>
</tr>
</tbody>
</table>
Does cancer represent a healthcare crisis – and why is it so difficult to intervene at all levels?
Healthcare Realities

• 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

- ~ 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)

Overall - Cancer Continues to Take Nearly the Same Toll as it did in 1950

Source for 2006 deaths and diagnoses: American Cancer Society (ACS) 2006 Cancer Facts & Figures; Atlanta, Georgia
And a Looming Global Healthcare Crisis

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

Self-sufficiency in growth signals

Evading apoptosis

Sustained angiogenesis

Immunologic tolerance

Insensitivity to growth signals

Tissue invasion and metastasis

Limitless replicative potential

Adapted from: Hanahan & Weinberg, Cell 100:57 (2000)
Tumors are Heterogeneity – A Major Barrier

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

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

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

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

Sub-Molecular
- Genome
- Transcriptome
- Proteome
- Epigenome
- Spatial/Micro-environments

Complex Systems
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 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

RTK/RAS/PI-3K signaling altered in 88%

- EGFR (Mutation, amplification in 45%)
- ERBB2 (Mutation in 8%)
- PDGFRA (Amplification in 13%)
- MET (Amplification in 4%

Mutation, homozygous deletion in 18%

NF1 → RAS

Mutation in 2%

PI3K → AKT

Mutation in 15%

PTEN (Mutation, homozygous deletion in 36%)

PI3K → FOXO

Mutation in 1%

P53 signaling altered in 87%

- Activated oncogenes
  - CDKN2A (Hippel-Lindau, mutation in 52%)
  - Homozygous deletion in 49%
  - CDK4
  - CCND2
  - CDK6

- Amplification in 18%
- Amplification in 2%
- Amplification in 1%

- MDM2 (Amplification in 14%)
- MDM4 (Amplification in 7%)

- TP53
  - Mutation, homozygous deletion in 35%
  - Senescence
  - Apoptosis

CDKN2B

Homologous deletion in 47%

CDKN2C

Homologous deletion in 2%

- RB1
  - G1/S progression

TCGA: Nature 2008
Harnessing New Knowledge - Four Subtypes of GBM Were Identified

A. TCGA Core Samples

<table>
<thead>
<tr>
<th>Proneural</th>
<th>Neural</th>
<th>Classical</th>
<th>Mesenchymal</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLL3</td>
<td>NKK2</td>
<td>SOX2</td>
<td>ERBB3</td>
</tr>
<tr>
<td>OLIG2</td>
<td>FBXO3</td>
<td>GABRB2</td>
<td>SNCG</td>
</tr>
<tr>
<td>DNMT1</td>
<td>TOP1</td>
<td>ABL1</td>
<td>BOP1</td>
</tr>
<tr>
<td>FGFR3</td>
<td>PDGFA</td>
<td>EGFR</td>
<td>AKT2</td>
</tr>
<tr>
<td>NES</td>
<td>CASP1/4/5/8</td>
<td>ILR4</td>
<td>CH13L1</td>
</tr>
<tr>
<td>TRADD</td>
<td>TLR2/4</td>
<td>RELB</td>
<td></td>
</tr>
</tbody>
</table>

B. Validation Samples

<table>
<thead>
<tr>
<th>Proneural</th>
<th>Neural</th>
<th>Classical</th>
<th>Mesenchymal</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLL3</td>
<td>NKK2</td>
<td>SOX2</td>
<td>ERBB3</td>
</tr>
<tr>
<td>OLIG2</td>
<td>FBXO3</td>
<td>GABRB2</td>
<td>SNCG</td>
</tr>
<tr>
<td>DNMT1</td>
<td>TOP1</td>
<td>ABL1</td>
<td>BOP1</td>
</tr>
<tr>
<td>FGFR3</td>
<td>PDGFA</td>
<td>EGFR</td>
<td>AKT2</td>
</tr>
<tr>
<td>NES</td>
<td>CASP1/4/5/8</td>
<td>ILR4</td>
<td>CH13L1</td>
</tr>
<tr>
<td>TRADD</td>
<td>TLR2/4</td>
<td>RELB</td>
<td></td>
</tr>
</tbody>
</table>

Verhaak et al., submitted
The Major Barriers – Where Nanotechnology can Provide New Insights and Capabilities

• 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

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.

![Diagram showing nanometer scales and various nanotechnology structures](image)
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

<table>
<thead>
<tr>
<th>Concentration</th>
<th>Molecule/Drop</th>
<th>Detection/Targets/Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>$10^{-3}$- Millimolar</td>
<td>Quadrillions</td>
<td>Colorimetric/Enzymatic Chemistry Blood Sugar (Diabetes)</td>
</tr>
<tr>
<td>$10^{-6}$- Micromolar</td>
<td>Trillions</td>
<td>ELISA &amp; Chemiluminescence Troponin, CK-MB, BNP, $\beta$HCG</td>
</tr>
<tr>
<td>$10^{-9}$- Nanomolar</td>
<td>Billions</td>
<td>Bio-barcode Technologies Cancer: Prostate, Ovarian, Breast</td>
</tr>
<tr>
<td>$10^{-12}$- Picomolar</td>
<td>Millions</td>
<td>Alzheimer’s Disease, Mad Cow Pulmonary Disease, Cardiovascular</td>
</tr>
<tr>
<td>$10^{-15}$- Femtomolar</td>
<td>Thousands</td>
<td>Disease</td>
</tr>
<tr>
<td>$10^{-18}$- Attomolar</td>
<td>Tens</td>
<td></td>
</tr>
<tr>
<td>$10^{-21}$- Zeptomolar</td>
<td>&lt;1</td>
<td></td>
</tr>
</tbody>
</table>
Nanotechnology Holds Significant Promise for Cancer Detection, Treatment, Prevention:

- Target Identification and Validation
- Lead Development
- Animal Studies
- Clinical Trials
- High content cellular assays
- Real-time therapeutic monitoring
- Ultrasensitive biomarker detection
- Contrast and optical imaging agents
- Multifunctional targeted nanoparticles
- Early detection
- Diagnosis
- Treatment
- Patient care
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

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

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)

- Nanotechnology Platform for Pediatric Brain Cancer Imaging and Therapy, University of Washington, Seattle, Wash.
- Novel Cancer Nanotechnology Platforms for Photodynamic Therapy and Imaging, Roswell Park Cancer Institute, Buffalo, N.Y.
- Multifunctional Nanoparticles in Diagnosis and Therapy of Pancreatic Cancer, State University of New York, Buffalo, N.Y.
- DNA-linked Dendrimer Nanoparticle Systems for Cancer Diagnosis and Treatment, University of Michigan, Ann Arbor, Mich.
- Hybrid Nanoparticles in Imaging and Therapy of Prostate Cancer, University of Missouri, Columbia, Mo.
- Metallofullerene Nanoplatform for Imaging and Treating Infiltrative Tumor, Virginia Commonwealth University, Richmond, Va.
- Near-Infrared Fluorescence Nanoparticles for Targeted Optical Imaging, University of Texas M. D. Anderson Cancer Center, Houston, Texas
- Emory-Georgia Tech Nanotechnology Center for Personalized and Predictive Oncology, Atlanta, Ga.
- Carolina Center of Cancer Nanotechnology Excellence, University of North Carolina, Chapel Hill, N.C.

Centers of Cancer Nanotechnology Excellence (8)

Cancer Nanotechnology Platform Partnerships (12)
Common Data Storage - caNanoLab Database

- 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

- standardization of materials characterization
- acceleration of clinical translation

Sources of Nanomaterials
- Centers of Cancer Nanotech Excellence (CCNEs)
- Academia
- Big Pharm
- Small Biotech
- NCI, NIH, NSF Grants
- DoD, DoE
- Unconventional Innovative Program (UIP)

Close interface with NIEHS

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

- More than 165 individual nanoparticles undergoing characterization
  - 50 Active collaborations (MTAs)
  - In 2008, 14 new MTAs, 13 CDAs, 1 CRADA with GE
  - 45 animal studies to date
Timeline: Moving into second phase of Cancer Nanotechnology

2004
- Cancer Nanotechnology Plan Published
- NCL Launches
- NCI Alliance for Nanotechnology in Cancer

2005
- Program Renewed
- RFA Released

2006
- Evaluation and Update
  - Scientific Output: Over 1000 pubs
  - Clinical Translation: 50 companies, Over 200 patents, 8-10 clinical trials

2007
- NCI Alliance for Cancer Nanotechnology in Cancer

2008
- Phase II Clinical Focused

2009
- Nano Imaging
- Nano Diagnostics
- Nano Therapy

2010
- Basic
- Translational
- Pre-Clinical
- Clinical

Scientific Output
- Over 1000 pubs

Clinical Translation
- 50 companies
- Over 200 patents
- 8-10 clinical trials

Nano Imaging
- Nano Diagnostics
- Nano Therapy
NCI Alliance for Nanotechnology in Cancer – Open Competition Phase II (Organizational Structure)

- Centers for Cancer Nanotechnology Excellence (CCNE) U54 Cooperative Agr.
- Cancer Nanotechnology Platform Partnerships U01 Cooperative Agr.
- Multi-disciplinary Training K99/R00 Awards, R25 Awards
- Nanotechnology Characterization Laboratory

- Coordination and Governance Committee
- Industrial Advisory Committee
- Clinical Advisory Committee
- NIH Cancer Nanotechnology Working Group

NCI Divisions

Awards Fall, 2010
http://nano.cancer.gov

• 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

Nanotechnology in Cancer

NCI Alliance for Nanotechnology in Cancer

Science, 2008
Nanotechnologies are Addressing Toxicity - Delivery – Efficacy Barriers in Drug Development

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

~ US$ 1 Billion
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).

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.

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.

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

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

Lab Chip 9, 2016 (2009)
Nature Biotech 26, 1373 (2008)
Formulation of targeted nanoparticle-containing siRNA:
- Water-soluble, linear cyclodextrin-containing polymer
- Adamantane-PEG conjugate
- Targeting component (human transferrin)

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

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

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

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

<table>
<thead>
<tr>
<th>Company</th>
<th>Product(s)</th>
<th>Material</th>
<th>Indication</th>
<th>Status</th>
<th>Admin.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced Magnetics</td>
<td>Combidex</td>
<td>Iron oxide nanoparticles</td>
<td>Tumor imaging</td>
<td>Conditional FDA approval</td>
<td>IV</td>
</tr>
<tr>
<td>Avidimer</td>
<td>Platform, ATI-001</td>
<td>Targeted dendrimers</td>
<td>Various cancers</td>
<td>Pre-clinical</td>
<td>IV</td>
</tr>
<tr>
<td>BIND</td>
<td>Platform technology</td>
<td>Targeted PLGA-PEG nanoparticles</td>
<td>Prostate cancer, others</td>
<td>Pre-clinical</td>
<td>IV</td>
</tr>
<tr>
<td>Carbon Nanotechnology</td>
<td>DF1</td>
<td>Dendritic fullerene</td>
<td>Chemoprotection</td>
<td>Pre-clinical</td>
<td>IV</td>
</tr>
<tr>
<td>Dendritic Nanotechnologies</td>
<td>Dendrimer-Magnevist</td>
<td>PAMAM dendrimer</td>
<td>MRI imaging agent</td>
<td>Pre-clinical</td>
<td>IV</td>
</tr>
<tr>
<td>ImaRx Therapeutics</td>
<td>MRX-951</td>
<td>Self-assembling block copolymer</td>
<td>Cancer</td>
<td>Pre-clinical</td>
<td>IV</td>
</tr>
<tr>
<td>Kereos</td>
<td>Platform technology</td>
<td>Perfluorocarbon polymers</td>
<td>Cancer and cardiovascular</td>
<td>Starting Phase I</td>
<td>IV</td>
</tr>
<tr>
<td>Liquidia Technologies</td>
<td>Platform technology</td>
<td>PRINT™ nanoparticles</td>
<td>Cancer, others</td>
<td>Pre-clinical</td>
<td>IV</td>
</tr>
<tr>
<td>Triton Biosystems</td>
<td>TNT-Anti-Ep-CAM</td>
<td>Polymer-coated iron oxide</td>
<td>Solid tumors</td>
<td>Pre-clinical</td>
<td>IV</td>
</tr>
</tbody>
</table>
Nanotechnology is an Enabler of New Solutions for Cancer

- **Detection**
  - Target molecule
  - Probe molecule
  - Gold
  - Silicon nitride microcantilever

- **Imaging**
  - Target binding
  - Deflection

- **Therapy**
  - Localization
  - 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

- 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
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

KZERO CONSULTING

Technology Adoption Curve

Innovators 2.5% gp
Early adopters 13.5%
Early majority 34%
Late majority 34%
Laggards 16%

Adoption gap
Why Nanotechnology for Personalized Cancer Medicine?

- 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**