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
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


Nanotechnology will allow for the development of:
- Highly accurate *in vitro* and *in vivo* sensors
- Novel imaging contrast agents
- Platforms for localized therapy

**Treatment Effectiveness**

1) ‘Nano’ *in vitro* sensors → Earlier diagnostics
2) Traditional therapy

1) Quantitative *in vivo* nano-sensors → Further improved diagnostics
2) Localized nano-therapy → More effective treatment Reduced side effects
CSSI Strategy to Accomplish Goals of Contemporary Science

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

• **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

2007 2008 2009 2004 2003
0 100 200
# publications

2003 04 05 06 07 08 09

Cancer AND Nanotechnology AND Therapy

2007 2008 2009 2004 2003
0 100 200
# publications

2003 04 05 06 07 08 09

Cancer AND Nanotechnology AND Diagnosis

2007 2008 2009 2004 2003
0 40 80 120
# publications

2003 04 05 06 07 08 09

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

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

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.

Focus on cancers with low survival rates such as brain, lung, pancreas, and ovarian cancer
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 (CCNE) U54 Cooperative Agr.
- Cancer Nanotechnology Platform Partnerships U01 Cooperative Agr.
- Multi-disciplinary Training K99/00 Awards, R25 Awards
- Nanotechnology Characterization Laboratory
- Coordination and Governance Committee (CGC)
- Industrial Advisory Board (IAC)
- Clinical Advisory Committee (CAC)
- NIH Working Group
- Other NCI Programs
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

- 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

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

Early detection tests
EDRN report, 08
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


Pro-drug strategy


Hyperthermia

Photothermal

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

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

Genetic therapy

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

M. Davis – Caltech-UCLA CCNE
Screening for Colorectal Cancer
Step up from Colonoscopy

1-mm diameter collimated Illumination beam
Variable working distance ~ 0.5 to 1.5 cm

6 mm diameter instrument channel

10 mm

therapeutic endoscope

3 to 5 mm diameter

1 single mode Illumination Fiber
(5 micron core and 120 micron cladding)

36 multimode fibers
(200 micron core and 40 micron cladding)

Sam Gambhir et al.
Stanford University

Step up from Colonoscopy

Sam Gambhir et al.
Stanford University
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
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

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

• Collaborations within NIH, FDA, NIST, NIEHS
  - NTP, EPA and others.

• Standards development efforts in collaboration with NIST, ASTM, ISO, IANH

• Inter-laboratory Studies

• caNanoloab 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, \textit{in vitro}, and \textit{in vivo} characterizations as well as protocols
  - 28 protocols for nanoparticle characterization assays
  - 650 nanoparticle formulations
  - 2411 characterization
    - 787 physico-chemical
    - 1538 \textit{in vitro}
  - More than 1100 publications

https://wiki.nci.nih.gov/display/ICR/caNanoLab
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
• Devices to diagnose the disease
• Devices to treat the disease
• Devices to monitor the disease in post-treatment stage
• 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
Krzysztof Ptak
Nicholas Panaro
Sara Hook
George Hinkal

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