The Workings of NCI Nanotechnology Alliance for Cancer – an Opportunity for a New Class of Diagnostic and Therapeutic Solutions Based on Nanotechnology

nanoUtah 2007
October 26, 2007

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National Cancer Institute
Unlike Other Major Disease Killers, Cancer Continues to Take the Nearly Same Toll As In 1950

- Cerebrovascular Diseases: 180.7 (1950), 53.3 (2003)

Source for 2005 deaths and diagnoses: American Cancer Society (ACS) 2005 Cancer Facts & Figures; Atlanta, Georgia
Nanotechnology is a “disruptive technology” which will drive a new generation of cancer diagnostic and therapeutic products, resulting in dramatically improved cancer outcomes.

- Early detection – highly sensitive and specific sensors
- In-vivo imaging – new contrast agents, localization
- Therapeutics – local, on-particle delivery
Nanotechnology is an Enabler of New Solutions for Cancer

**Focus Areas:**

- Molecular imaging and early detection
- In vivo imaging
- Reporters of efficacy
- Multifunctional therapeutics
- Prevention and control
- Research enablers

**Early detection**

**Imaging**

**Therapy**
Highly talented multi-disciplinary research teams

Sciences, medicine, and engineering

Competition and collaboration

Synergy and difference

Can we build a bigger whole?

• promote the development of state-of-the-art nanotechnologies for cancer applications
• accelerate the translation of the discoveries into clinically relevant diagnostics and therapeutics
Major Programs of the Alliance:

1. Centers of Cancer Nanotechnology Excellence
2. Multidisciplinary Research Teams
   - Training
   - Interagency Collaborations
3. Nanotechnology Platforms for Cancer Research
4. Nanotechnology Characterization Laboratory
Clinical Applications Using Nanoparticles

- Nanoparticles
  - Quantum dots
  - Polymer particles
  - Dendrimers
  - Magnetic particles
  - Nanoshells
  - Nanotubes
  - Virus engineered particles

- Multiple functions
  - Tissue targeting
    - Tumor-specific binding
  - Sensing or imaging capability
    - Improved sensitivity
    - Multi-modal imaging
  - Non-invasive treatment
    - Therapeutic localized delivery
    - Localized cell kill
    - Lower dose administered
    - Improved side effect profile
Nanotechnology will allow for the development of:

- Highly accurate in-vitro and in-vivo sensors and
- Platforms for localized therapy
Multiplexed Diagnostic Assays

Q-dots

Alivisatos et al.

Nanocrystals for E-chem det.

J. Wang, Analytica Chimica Acta 500 (2003) 247

In-vitro Diagnostic Biomarker Recognition

Nanorods

Nicewarner-Pena et al., Science 294, 137 (2001)

Cantilevers

G. Wu and A. Majumdar, Nature Biotech 19, 856 (2001)
1. Up to one million times more sensitive than conventional ELISAs.

2. Evaluate new biomarkers for diagnosing and following human diseases (e.g. Cancer, HIV, Alzheimer’s Disease).


Microfluidics for Diagnostics

Quantum Dots for In-vivo Imaging


*In vivo* fluorescence images of tumor using QD probes

- Human prostate cancer growing in nude mice
- QDs functionalized with PSMA
- Wide range of wavelength coverage using different materials


Multi-color imaging using the same excitation source
Nanoparticles (dextran-coated iron oxide crystals, Combidex) injected into the circulation travel to the lymph nodes. Metastatic tumors growing in the nodes interfere with particle distribution, and this is detectable by MRI. 80 men undergoing surgery or biopsy for prostate cancer had MRI exams both with and without the nanoparticles before surgery. 33 of the men actually had metastatic lymph nodes. MRI with the particles identified all 33, whereas MRI without the particles missed more than half of them.

Ralph Weissleder (MGH, Harvard Medical School)
Jean de la Rosette (Netherlands)
MRI Detection of Tumor Derived Cells via Proteolytic Actuation of Nanoparticle Assembly

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

Multi-Functional Nanoparticle-based Therapies

- Multi-functional platforms:
  - Targeting
  - Delivery
  - Reporting, biosensing

In one package

Free drug formulations do not possess multi-functional characteristics

First generation of nano-delivered drugs (no targeting) approved by FDA – Abraxane®

Nanoparticle-based Therapies: Different Approaches

Dendrimers:
Targeted delivery of methotrexate

Nanoshells:
Photothermal therapy

J. Baker, et al., Cancer Res. 65, 5317 (2005)
N. Halas, J. West et al., Ann Biomed Eng. 34, 15 (2006)
Free MTX 30 mg/kg total

Nanodevice MTX 3 mg/kg total MTX

Kukowska-Latallo, Baker et al., Cancer Research, 65, 5317 (2005)
Aptamers are non-immunogenic chemically processed DNA or RNA oligonucleotides that bind to antigen with high affinity and specificity; nanoparticle-aptamer conjugates have been developed for Prostate Specific Membrane Antigen (PSMA).

NP-Apt conjugates show greater efficacy in a xenograft mouse model than non-targeted nanoparticles.
The anti-cancer agent is conjugated to a biocompatible polymer via an ester bond. The linkage is hydrolysed by cancer-specific enzymes or by high or low pH at the tumor site, at which time the nanoparticle releases the drug.

PRINT™ Particles: CDI-Activated PEG for Functional Targeting

Multiplexed Delivery of Targeted Anticancer Agents

Joe DeSimone, UNC
Current Status

- Development of new diagnostic and therapeutic platforms is at different levels of maturity
- Two drugs approved by FDA: 1) Abraxane – paclitaxel bound to albumin (American Pharmaceutical Partners) and 2) Doxil – liposome encapsulated doxorubicin
- Common scheme for therapeutics – use existing drugs and adapt them to nano-based delivery platform
- In-vitro diagnostic tools evaluate clinical samples
- Several companies (2-5) ready to file IND within next 12 months
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<th>Company</th>
<th>Product(s)</th>
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<td>Albumin-bound paclitaxel</td>
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<td>Combidex</td>
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Priorities and Wish List

• Biomarker libraries
• Novel and more effective approaches to tumor targeting
• Multiplexed sensors with high sensitivity and specificity
• Multi-modality constructs for imaging
• Therapy – localized delivery should result in lower site effects. Would it result in more effective treatment?
• Nanotechnology and prevention
• Tools to monitor and understand metastasis
• Predictive modeling tools
Acknowledgements:
NCI Nanotechnology Program Office

Travis Earles
Linda Molnar
Jerry Lee
Larry Nagahara