Cancer Nanotechnology – Opportunities and Challenges – View from the NCI Alliance for Nanotechnology in Cancer

NNI Strategic Plan & Opportunities Workshop
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Burden of Cancer

- 556,900 American will die of cancer this year
- 1,372,900 Americans will be diagnosed with cancer this year
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
Scientific output – over 1000 peer-reviewed journal papers published with an 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
Particle Replication In Non-Wetting Templates

- a soft lithographic imprint technique
- below 50 nm precision
- controlled structural char. (shape, size, composition)
- controlled functional char. (cargo, surface structure)

In biological systems, PRINT particles:
- Internalize
- Deliver specific cargo (therapeutics, imaging agent, multifunctional materials)

Effects of size, shape and aspect ratio on internalization
- preferential cellular uptake of cylindrical NPs

J. DeSimone – U. North Carolina CCNE
PNAS (2008) 105: 11613
WIRES (2009) 1: 291
Approach:
• Docetaxel delivery to prostate cancer
• Aptamer recognizing PSMA on prostate cancer cells (LNCaP cell line)
• The comparative efficacy study of intratumoral injection (40 mg/kg) was evaluated over 109 days

Polymeric platform for drugs or biologics delivery
- Targeting ligand → aptamers (nonimmunogenic, stable in a wide pH range & temperature)
- Surface functionalization → PEG (increased stability)
- Polymer matrix → PLGA (controlled released polymer)
- Therapeutic payload → small molecules, peptides or nucleic acids

**Advantage:** increased efficacy & reduced toxicity

Targeted NPs are more effective in tumor size reduction

100% of the targeted NPs group was alive on day 109

Langer & Farokhzad – MIT – Harvard CCNE

PNAS (2006) 103: 6315
PNAS (2008) 105: 2586
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

Cyclodextrin-based siRNA delivery

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Deliver siRNA to reduce expression of RRM2

- RRM2 mRNA reduction
- RRM2 protein reduction

**Tissue analysis before and after injection**

M. Davis – Caltech-UCLA CCNE
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
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 - Calando Pharm. and Davis - Caltech
  - siRNA on polymeric nanoparticles - Calando Pharm. and Davis, Ribas, Czernin - Caltech
  - siRNA – Alnylam and Sharp - MIT
Nanotechnology Characterization Laboratory: Serving the Community

NCL is a formal collaboration between NCI, FDA and NIST

Scott McNeil
Anil Patri
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.
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