Cancer Nanotechnology – Opportunity for Novel Therapeutics and Diagnostics

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NFAC meeting

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• **Scientific output** – over 500 peer-reviewed journal papers and close to 100 patents and patent submissions published

• **Clinical translation** – over 70 companies in the space of diagnostics and therapy are associated with the program. Majority of them are start-ups.
  - 16 clinical trials are associated with program projects
  - several companies are in pre-IND discussions with FDA
  - formed a consortium to involve large pharma and biotech companies to assist translational process

• **Provocative Questions RFA** – disproportionately large number of awards made to nanotechnology based proposals – total of 7: 6 R01s and 1 R21
Different Particles and Different Methods of Making Them

Why we formed NCL? - need for a comprehensive assay kit to evaluate different nanomaterials

- Covalent organic synthesis
  - Dendrimers, Polymers
- Self-assembly
  - Liposomes, Emulsions, Micelles
- Crystal formation
  - Metal nanoparticles, Quantum dots
- Laser ablation, CVD
  - Fullerenes, carbon nanotubes
- Grinding/milling/fabrication
  - Organic and Inorganic Crystals
Nano-therapy Strategies

Delivery of chemotherapeutics


Delivery of siRNA


Hyperthermia

Photothermal

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

RF-heated

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

50 - 200 nm

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
Comparison of Delivery Profiles for Docetaxel with and without NPs

- Long-circulating particles and controlled drug release provide for well-controlled and differentiated PK profile across species
- sb-DTXL elimination from plasma occurs very quickly
Phase I Clinical Trial – Patient’s Data

Combination Therapies Using Nanoparticles

**Multiple drugs in one NP**
- delivery of a correct ratio of each drug to the target;
- synergistic therapeutic effects;
- ability to control drug exposure temporally


In vitro release kinetics in PBS from NPs
Nanotechnology Drug Delivery Strategies

Current
• Using nanoparticles to deliver established chemotherapeutic drugs while enhancing their efficacy
• Existing drugs are readily available and provide a direct, established comparator

Challenge
• Can we ‘resurrect’ drugs which have high potency, but also high toxicity and failed in free form delivery using nanoparticle-based delivery?

Action plan
• Proposing a joint development with DCTD to look at few drugs from NCI stockpile.
In vitro diagnostics and nanotechnology

- Modular diagnostics – work with bodily fluids, such as blood, serum, urine, or saliva
- Multiplexing – interrogate several biomolecular signatures at the same time
- Techniques to monitor and capture circulating tumor cells from blood
- Multifunctional capabilities – one platform capable of detecting nucleic acid and protein

• IBBC - microfluidic device for multiplexed detection of proteins in whole blood sample
• DEAL - single-strain (ss) DNAs bound to antibodies that are labeled with complementary ssDNA oligomers
• Currently tested for molecular and functional analysis of prostate, breast, melanoma, and glioblastoma
• Less than 10 min working time

Multiplexed protein measurements of clinical patient sera, (a) Layout of the barcode array used in this study, (b) Representative fluorescence images of barcodes used to measure the cancer marker PSA and 11 cytokines from cancer patient serum samples. B - samples from breast cancer patients; P - samples from prostate cancer patients, (c) Distribution of estimated concentrations of PSA, TNF-α and IL-1β in all serum samples. The horizontal bars mark the mean values.
Monitor secretion of proteins from individual cells to assess effectiveness of therapies

Shin, et al., *ChemPhysChem* 2010 (molecular patterning for these chips)
Shin, et al., *Biophys J* 2011 (macrophage secretome, information theory)
Ma, et al., *Nature Medicine*, 2011 (applied to melanoma immunotherapy patients)
Initiation and planning

Development of assay cascade

Receipt of materials

Characterization, SAR studies, Support of early development

At capacity, More mature concepts Work with NIEHS

ANNEX 2
NATIONAL CANCER INSTITUTE
NANOTECHNOLOGY CHARACTERIZATION LABORATORY
MATERIAL TRANSFER AGREEMENT
The National Cancer Institute (NCI) Nanotechnology Characterization Laboratory (NCL) has been designed to investigate the use of nanoparticulate material for the advancement of cancer research. This Material Transfer Agreement (MTA) permits the exchange of materials and associated information between NCI and the party defined below as “Provider.”
Supplemental Slides
Centers of Cancer Nanotechnology Excellence (U54)

- Carolina Center of Cancer Nanotechnology Excellence, University of North Carolina, Chapel Hill, NC
- Nanosystems Biology Cancer Center 2, California Institute of Technology, Pasadena, CA
- Nanomaterials for Cancer Diagnostics and Therapeutics, Northwestern University, Evanston, IL
- MIT-Harvard Center of Cancer Nanotechnology Excellence, Cambridge, MA
- Texas Center for Cancer Nanomedicine, University of Texas & MD Anderson, Houston, TX
- Johns Hopkins Center for Cancer Nanotechnology Excellence, Baltimore, MD
- Center for Translational Cancer Nanomedicine, Northeastern University, Boston, MA
- Dartmouth Center for Cancer Nanotechnology Excellence, Dartmouth College, Hanover, NH
- Center for Cancer Nanotechnology Excellence and Translation, Stanford University, Palo Alto, CA
- Dartmouth Center for Cancer Nanotechnology Excellence, Dartmouth College, Hanover, NH
- Johns Hopkins Center for Cancer Nanotechnology Excellence, Baltimore, MD