Nanotechnology Characterization Laboratory (NCL)

A Comprehensive Resource for Preclinical Evaluation of Nanomaterials

Scott E. McNeil
NCI-Frederick Advisory Committee (NFAC)
Sept. 12th, 2012

ncl@mail.nih.gov

NATIONAL CANCER INSTITUTE

Frederick National Laboratory for Cancer Research

Advanced Technology Program

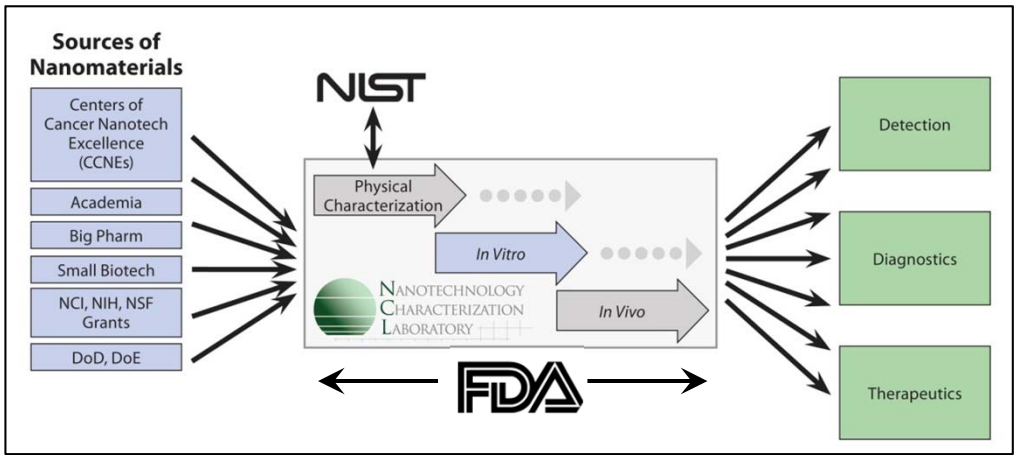
SAIC Frederick

Funded by NCI Contract HHSN261200800001E

NCL Concept of Operations

- The NCL was established in 2004 as an interagency collaboration among NCI, NIST, and FDA. The lab's mission is to accelerate the translation of promising nanotech cancer drugs and diagnostics.

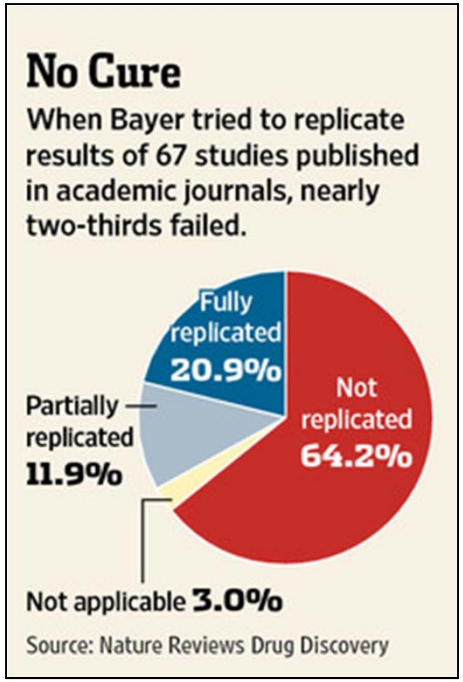
- NCL performs preclinical characterization of nanomaterials, including:
  - physicochemical characterization
  - in vitro experiments
  - in vivo testing for safety and efficacy.



90% of NCL's efforts support the extramural community.

Reproducibility

- Success rate of Phase 2 human trials (efficacy trials) down to 18% in 2008-2010.
- Bayer, Pfizer, Amgen, & other Pharma report difficulty replicating published research, “More often than not.”
- Increasing intricacy of experiments and sophisticated materials may exacerbate reproducibility challenges.



G. Naik, Scientists' Elusive Goal: Reproducing Study Results, Wall Street Journal, December 2, 2011

Prinz, Schlange & Asadullah, Believe it or not: how much can we rely on published data on potential drug targets? Nature Reviews Drug Discovery 10, 712, September 2011.

See also: Data Replication & Reproducibility, Special Issue of Science, 2 December 2011, Vol. 334, #6060.

NCL provides independent validation of results.

NCL Extramural Collaborators

NCI Alliance for Nanotechnology in Cancer

Dendritic Nanotechnologies, Inc.
A Starpharma Holdings Limited Company

CytImmune Sciences Inc

Johns Hopkins Medicine

Imperial College London

Penn State College of Medicine

Massachusetts Institute of Technology

LUNA Nanoworks
A Division of Luna Innovations Incorporated

Tego Bio Sciences

Alnis BioSciences, Inc.

Lombardi Comprehensive Cancer Center at Georgetown University

Arrowhead Research Corporation

PDS Biotechnology

Northwestern University

Azaya Therapeutics

BIND Biosciences

CNI

Carbon Nanotechnologies Incorporated

SignPath Pharma

Cedars-Sinai Medical Center

Synergene

City of Hope

Celator Pharmaceuticals

The University of Texas MD Anderson Cancer Center

University at Buffalo
The State University of New York

labopharm

Emory

Mizzou
University of Missouri-Columbia

Michigan

Northeastern University
Bouvé College of Health Sciences

USF University of South Florida
Department of Chemistry

UCLA

Kereos
Targeted Therapeutics and Molecular Imaging

Purdue University

Avidimer therapeutics

UCSB

Nanospectra

ProNAi

Stanford University

Bexion Pharmaceuticals

FNL Capabilities

NANOTECHNOLOGY CHARACTERIZATION LABORATORY

NCI Alliance for Nanotechnology in Cancer

From the Molecular Level, through In Vitro & In Vivo Screening, into Clinics…to the Cure!

In Vivo Screening
- ADME-Toxicity
- Efficacy
- Pharmacokinetics

In Vitro Screening
- Blood contact properties
- Toxicity
- Immune cell functions

Protein Expression Lab

Protein Chemistry Lab

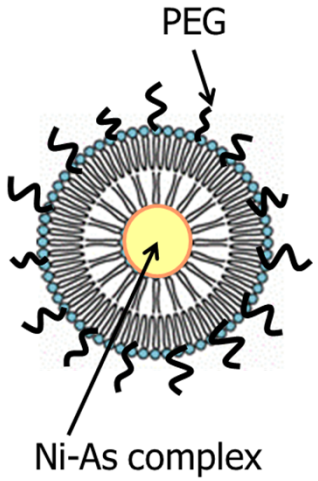
Characterization
- Size
- Composition
- Surface functionality
- Compatibility in biological matrices

Scale-Up Assistance
- Batch-to-batch consistency
- Process design and optimization
- Quality control
- Developing methods for in-process testing

Clinical Support Lab

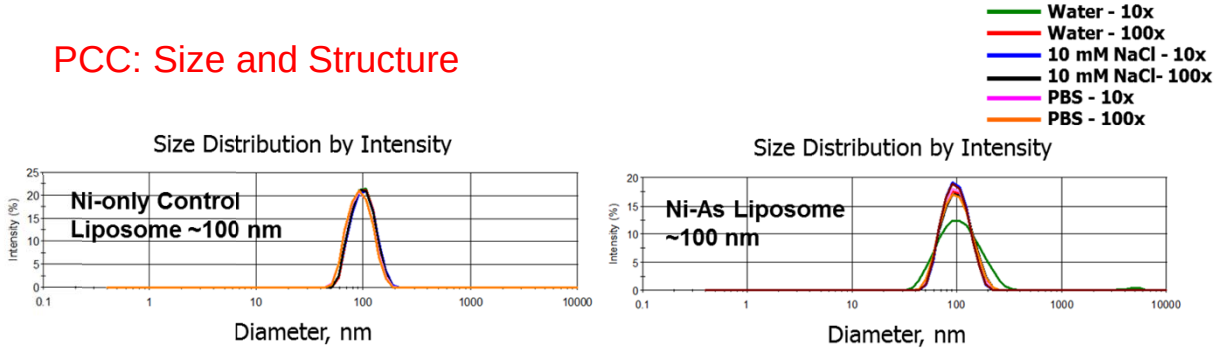
Analysis of Clinical Samples

NCL Characterization Case Study: Ni-As Liposomes

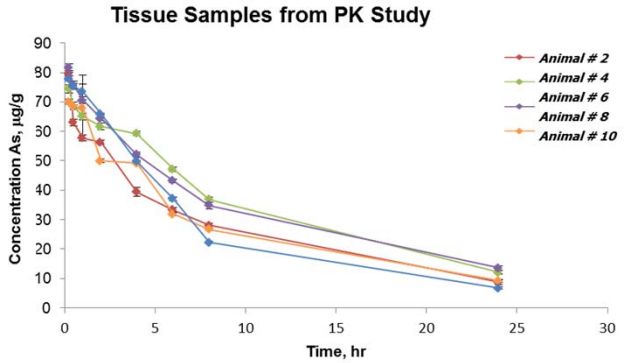


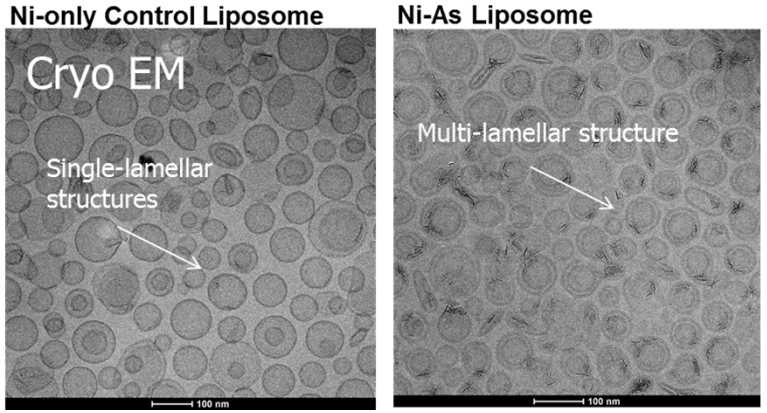
- NCL in vitro studies indicated the control (including the nickel counter ion) liposome was significantly toxic.
- NCL conducted characterization, in vivo tox and efficacy studies to see if this particle was also toxic in animals…

PCC: Size and Structure



PCC: ICPMS for Drug Quantitation



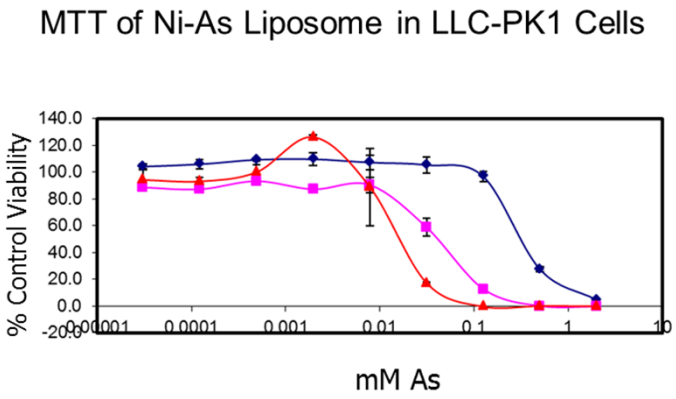


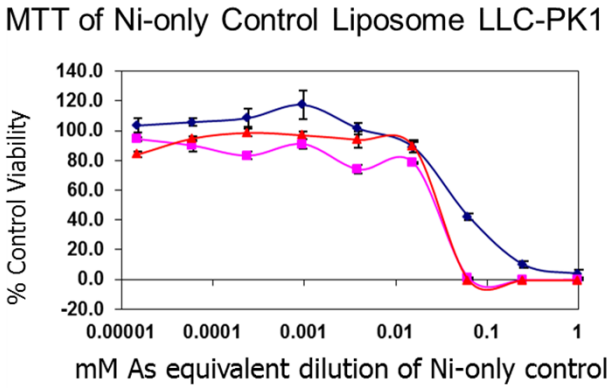
ICP-MS = inductively coupled plasma mass spectrometry; Ni = nickel; As = arsenic; PK = pharmacokinetics; PCC = physicochemical characterization

NCL Characterization Case Study: Ni-As Liposomes

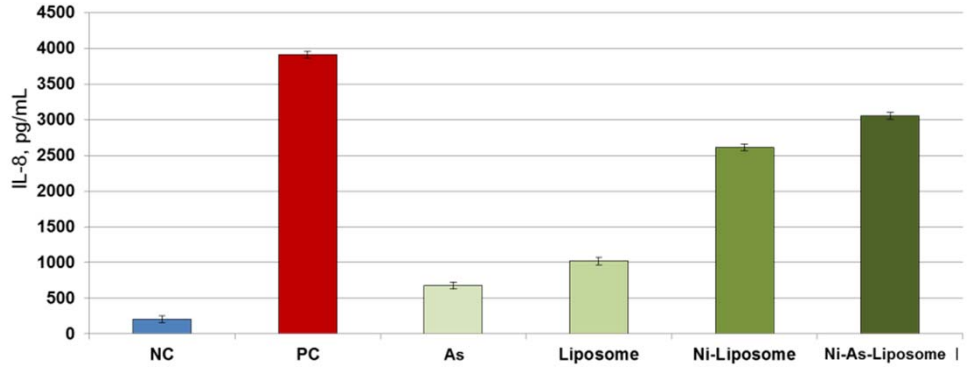
- NCL examined cytotoxicity and immunotoxicity of the formulation and controls in vitro.
- Much of the formulation's cytotoxicity and immunotoxicity was due to Ni rather than As API.

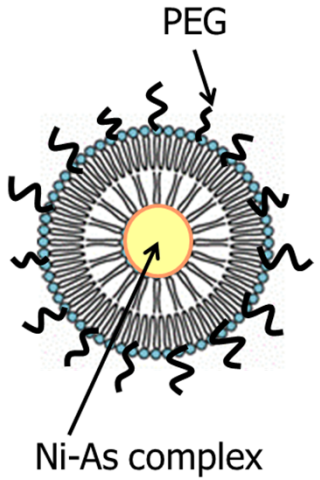
Cytotoxicity





Immunotoxicity



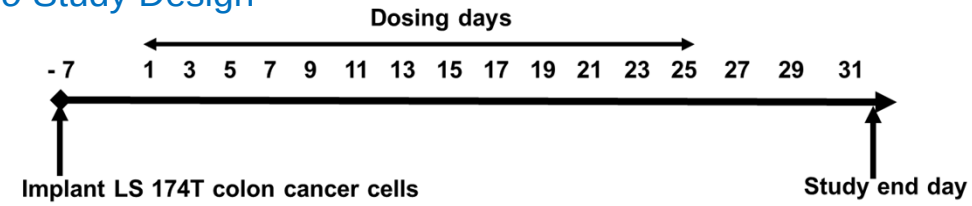


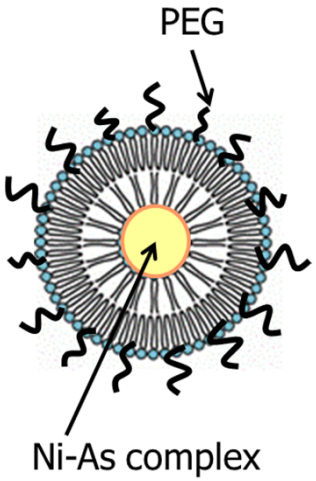
NC = negative control; PC = positive control; As = arsenic; Ni = nickel; LLC-PK1 = porcine renal proximal tubal cells; API = active pharmaceutical ingredient

NCL Characterization Case Study: Ni-As Liposomes

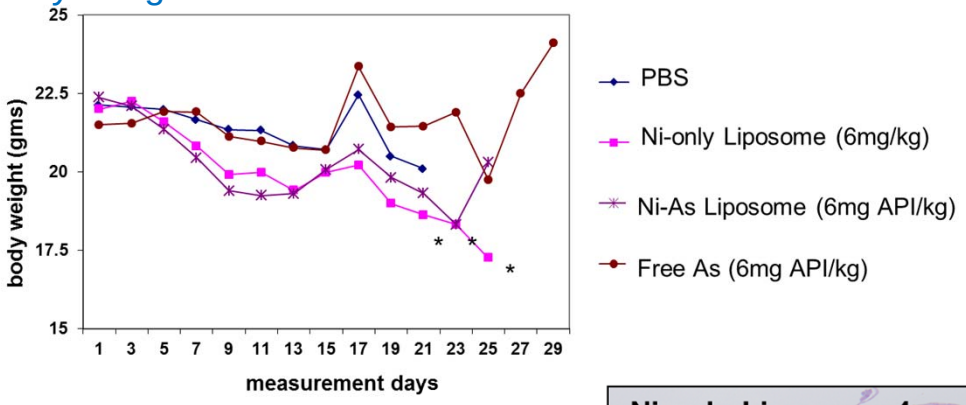
- NCL in vivo study showed the Ni-only liposome caused more body weight loss than the Ni-As-liposome.

In Vivo Study Design



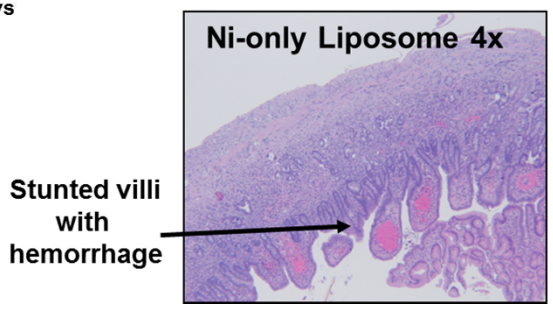


Animal Body Weight



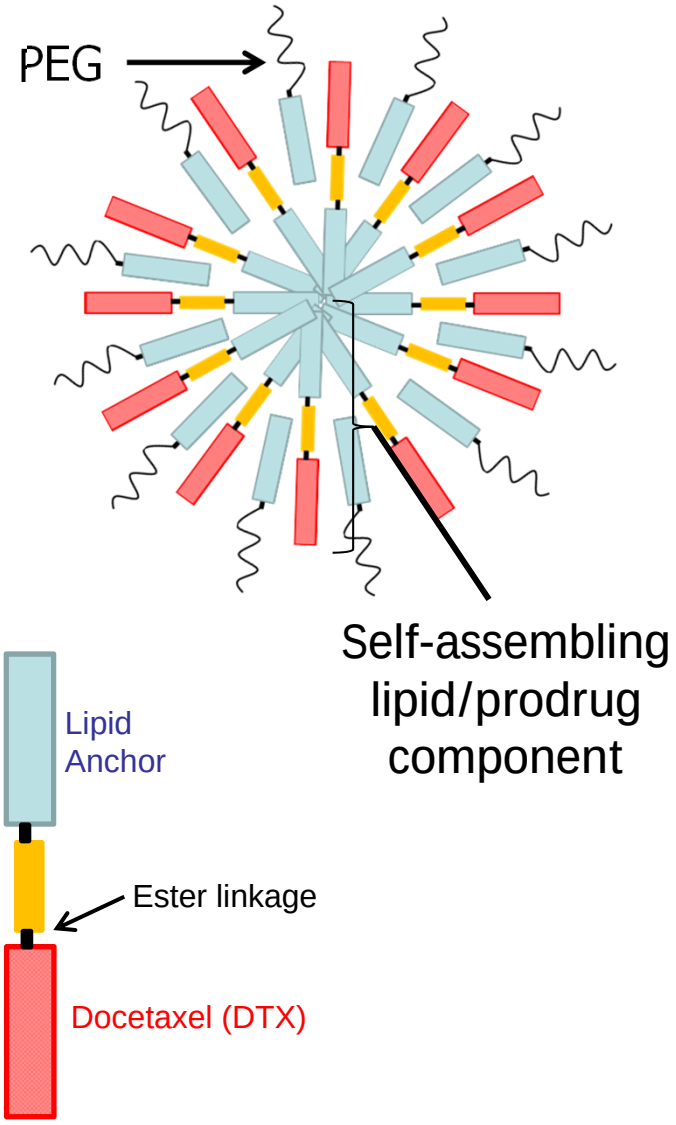
On NCL's recommendation, developer PI is now pursuing alternatives to Ni.

Histophathology of inflamation in duodenum



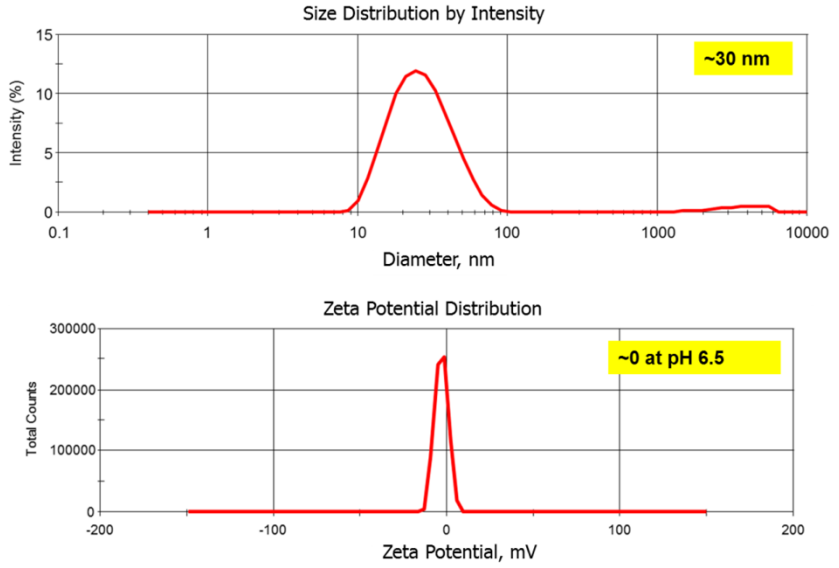
As = arsenic; Ni = nickel

NCL Characterization Case Study: Nanoparticle Prodrugs



- In theory, nanoparticle will get to tumor, prodrug will be released and DTX (API) cleaved/hydrolyzed.
- NCL characterized samples, measured in vitro plasma hydrolysis rates, in vivo PK, toxicity and efficacy.

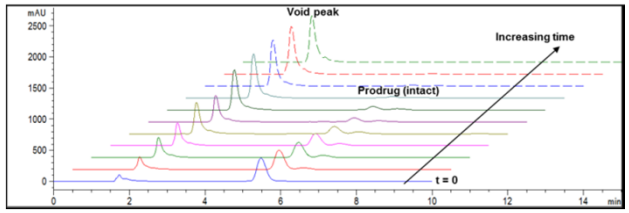
PCC: Size and Charge



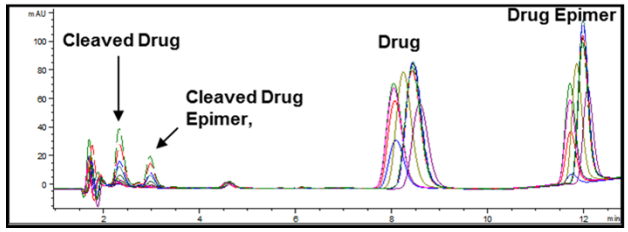
DTX = docetaxel; API = active pharmaceutical ingredient; PCC = physicochemical characterization; PK = pharmacokinetics

NCL Characterization Case Study: Nanoparticle Prodrugs

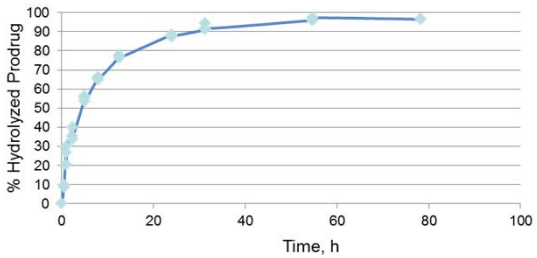
HPLC



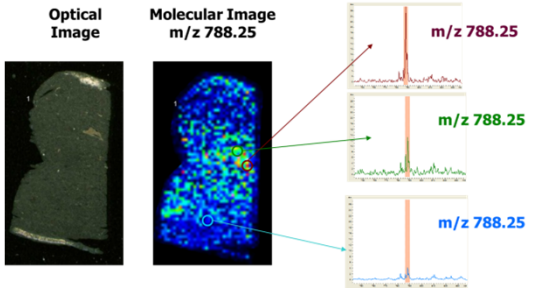
LC



In Vitro Prodrug Hydrolysis in Plasma

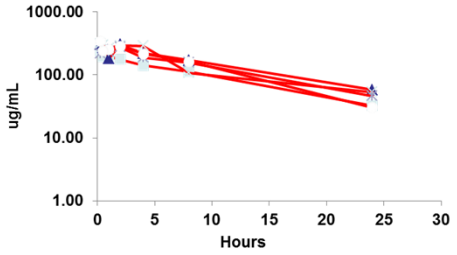


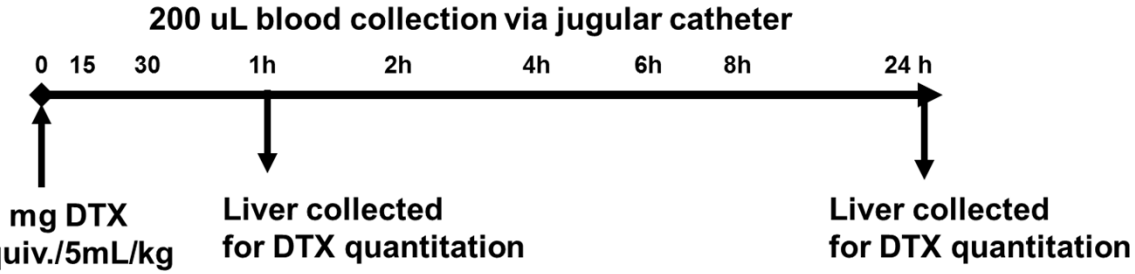
MALDI Liver Imaging



- NCL performed extensive characterization: HPLC to separate components of formulation and plasma. LC to determine cleavage site and drug stability.
- In vivo study to evaluate pharmacokinetics in jugular catheterized 10-wk-old female SD rats. Prodrug concentrations in plasma and liver measured w/ HPLC. MALDI imaging of liver.
- PK suggests distribution into plasma volume only (no tissue distribution). Plasma decay half-life approximately equal to hydrolysis half-life.

In Vivo Prodrug Plasma Profile

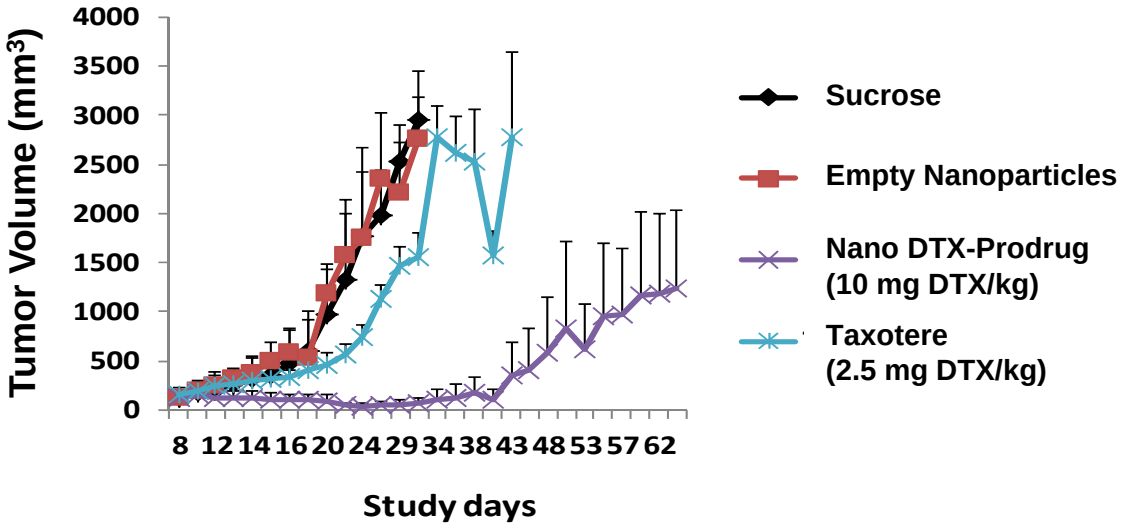




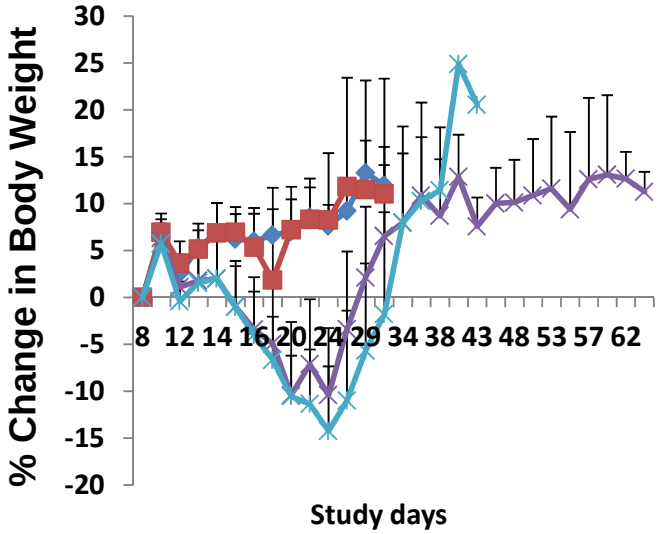
HPLC = high performance liquid chromatography; LC = liquid chromatography; SD = sprague dawley; DTX = docetaxel

NCL Characterization Case Study: Nanoparticle Prodrugs

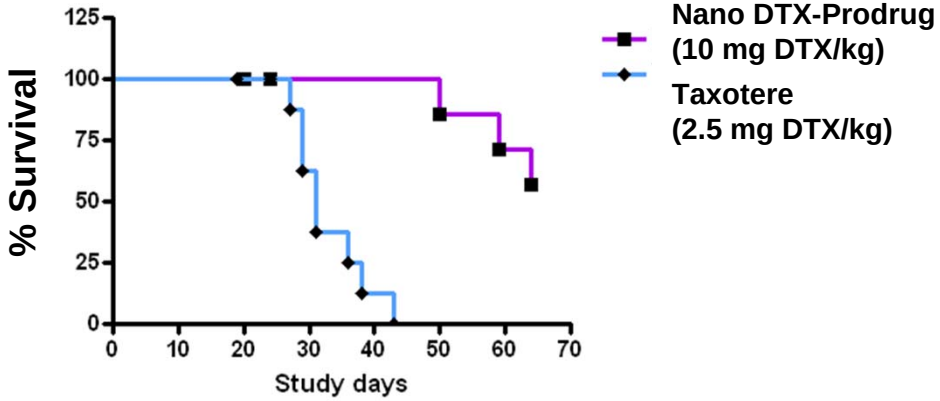
Tumor Volume



% Change in Body Weight



Animal Survival



More efficacious than an equi-toxic dose of Taxotere.

DTX = docetaxel

Success Stories:
NCL Submissions in Clinics

Nanotechnology Characterization Laboratory

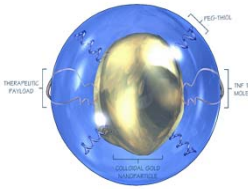
NCI Alliance for Nanotechnology in Cancer

Nanospectra

IDE 2008

- Silica-core gold-shell particle for photothermal ablation with NIR irradiation.
- Pilot safety study in head and neck cancers ongoing; efficacy study in lung tumors to start in 2012.

CytImmune Sciences Inc



Phase 1
Complete in 2008

- AurImune® PEGylated colloidal gold nanoparticle-TNFα conjugates.
- Phase II study in combination with Taxotere to start in 2012.

AZAYA THERAPEUTICS™

IND Dec 2009

- ATI-1123 PEGylated nanoliposomal formulation of docetaxel.
- Phase I safety study in patients with advanced solid tumors complete in 2012.

BIND BIOSCIENCES

IND 2011

- BIND-014 docetaxel-encapsulated PLGA nanoparticle-aptamer conjugates.
- Binds PSMA expressed on prostate cancer cells.
- Phase I safety study in patients with advanced or metastatic cancer ongoing.

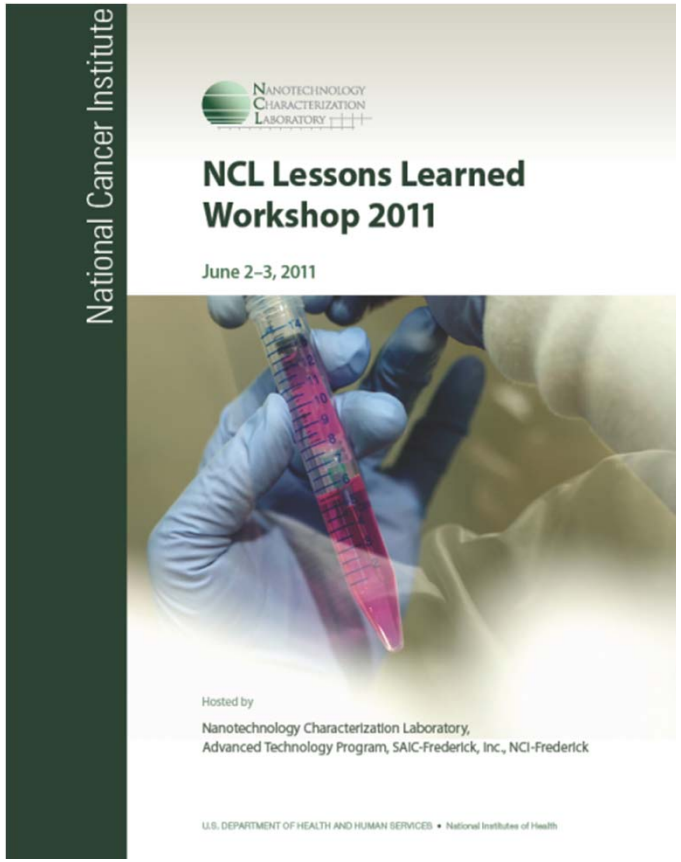
ProNAi

IND 2010

- PNT2258 liposome-encapsulated oligonucleotide for breast and lung cancer.
- Phase I safety study in patients with advanced solid tumors ongoing.

Getting Results Out to Community

- Lessons Learned Workshop:
  - Draws on NCL's experience with variety of nanomaterials, reagents, preparation methods, etc.
  - Presents negative results, "What doesn't work", not available elsewhere.
  - One-on-one discussions regarding specific nanoparticles/experiments/etc.
    - NIH, June 2011
    - FDA, Oct. 2011
    - Carolina CCNE, Dec. 2011.
    - Northeastern CCNE, Sept. 2012
    - Texas CCNE, Nov. 2012
    - Basel, Switzerland planned for 2013
    - More as possible…



Addressing Gaps in Translational Nanomedicine

- Scale up of nanomaterials to large scale production for clinical trials continues to be challenge.

- NCL assists in all aspects, without actually producing large scale batches in-house:
  - Batch-to-batch consistency testing
  - Process design and optimization
  - Quality control
  - Developing methods for in-process testing

NCL methods continue to become the de facto standard for nanomedicine community.

Nanotech Outside Oncology: NCL Work for Others

- NCL's expertise and resources now support other HHS agencies.
- Scientific Collaborations with FDA
  - Dermal penetration of nanomaterials in sunscreens and cosmetics, endotoxin, immune reactions.

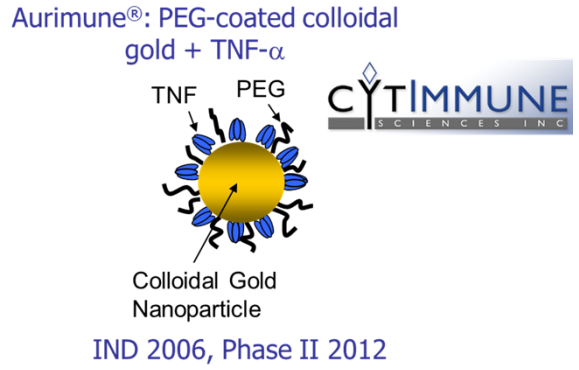
CDER
CBER
CDRH
CFSAN

- Collaboration with NIEHS for physicochemical characterization to support risk/hazard assessment
  - NCL provided key infrastructure support for NIEHS' U01/U19 nanotechnology centers of excellence

These collaborations contributed to over $1M/year in additional funding for NCL/NCI in FY11 & 12.

NCL Expertise is in Demand

- European Commission plans to construct “EU version” of NCL.
  - NCL playing an advisory role.
- FDA, EPA, DoD, routinely seeking NCL input on nanotech efforts.
- Approached by Big Pharma for characterization support and for nanotech reformulation of failed drugs.
  - Interest from Sanofi Aventis, J&J, Novartis, many others.



The NCL model has been extremely successful.

The NCL is now a leader in its field.

Acknowledgements

Nanotechnology Characterization Lab

Scott E. McNeil, Ph.D.
Anil K. Patri, Ph.D.
Stephan T. Stern, Ph.D., DABT
Marina A. Dobrovolskaia, Ph.D.
Nick Panaro, Ph.D.
Pavan Adiseshaiah, Ph.D.
Jeffrey D. Clogston, Ph.D.
Girija Chaubey, Ph.D.
Abdullah Mahmud, Ph.D.
Jennifer Grossman, Ph.D.
Rachael M. Crist, Ph.D.
Peng Zou, Ph.D.
Anna Ilinskaya, Ph.D.
Christopher B. McLeland, B.S., M.B.A.
Timothy M. Potter, B.S.
Barry W. Neun, B.S.
Sarah Skoczen, M.S.
Sonny Man, M.S.
Matthew Hansen, M.S.
Alpana Dongargaonkar, M.S.
Jamie Rodriguez, B.S.
David Parmiter, B.A.
Elizabeth Befekadu, B.S.
Lisa Sheffield

Electron Microscopy Lab

Ulrich Baxa, Ph.D.
Sarah Anderson, B.S.
Christina Burks, B.S.

Pathology/Histotechnology Lab

Diana C. Haines, D.V.M., DACVP
Gloryvee Rivera, B.S.
Wendi Custer, B.A.
Kelly Benauer

Contact Info:
Scott McNeil
(301) 846-6939
ncl@mail.nih.gov

http://ncl.cancer.gov

Funded by NCI Contracts N01-CO-12400 and HHSN261200800001E