NANOTECHNOLOGY CHARACTERIZATION LABORATORY

NCI Alliance for Nanotechnology in Cancer

NANOTECHNOLOGY CHARACTERIZATION LABORATORY

Lessons Learned and Future Directions

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

July 13, 2010

NCI-Frederick

Advanced Technology Program

SAIC From Science to Solutions

SAIC-Frederick, Inc.
A subsidiary of Science Applications International Corporation

NCI Cancer Nanotechnology Plan

NCL provides infrastructure support to the Alliance and to nanotech researchers - to overcome obstacles and translate “nano” into the clinical realm

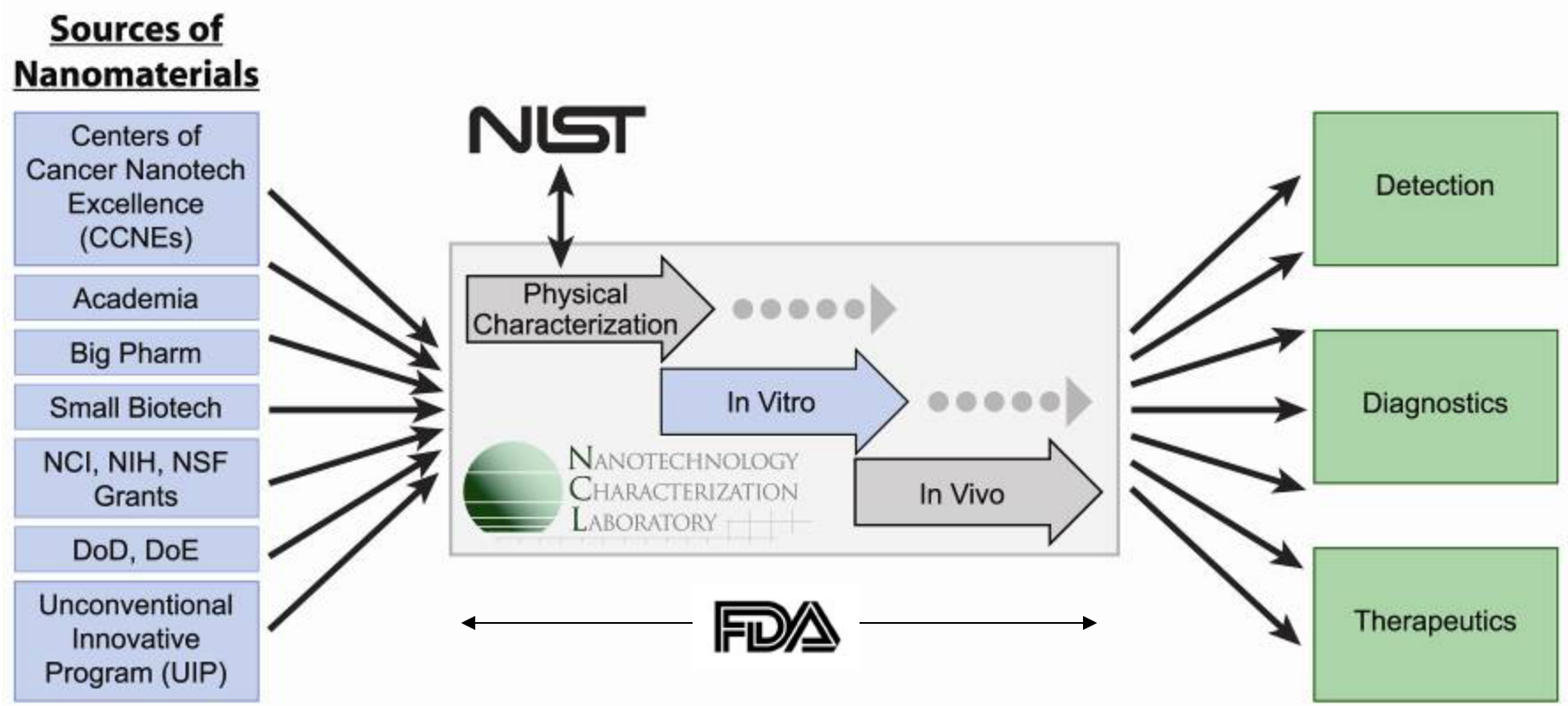
NCL Objectives

- Characterize nanoparticles using standardized methods
- Conduct structure activity relationships studies
- Facilitate regulatory review of nanotech constructs
- Engage in educational and knowledge sharing efforts

The NCL is a national resource available to investigators from academia, industry and government

ncl@mail.nih.gov
http://ncl.cancer.gov

NCL Concept of Operations



NCL is a formal collaboration among NCI, FDA and NIST

http://ncl.cancer.gov

NCL Timeline

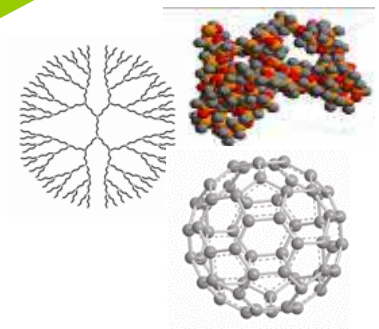
Characterization, SAR studies, support of early development

FY '07-'10

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."

Receipt of materials

FY '06



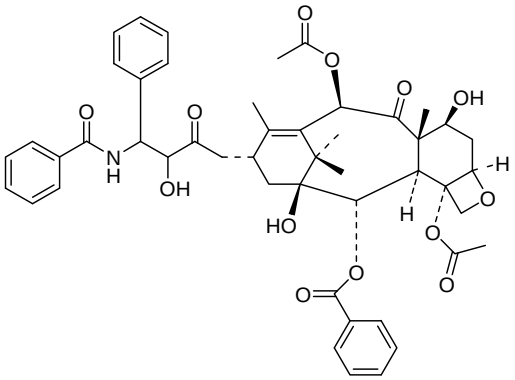
Development of assay cascade

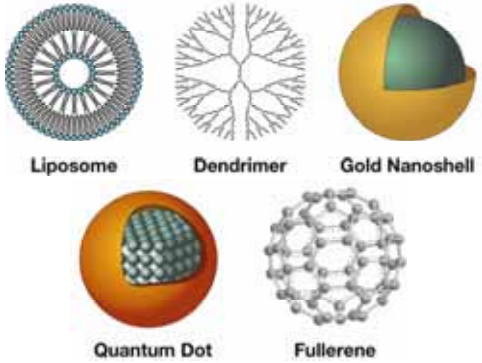
FY '05

Initiation and planning

FY '04

Physicochemical Characterization





Small molecules

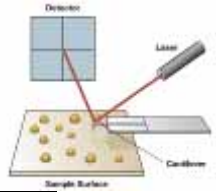
- Elemental analysis
- Mass Spec
- NMR
- UV-Vis
- IR
- HPLC
- GC
- Polarimetry

Physicochemical Parameters

- **Composition**
- **Physical properties**
- **Chemical properties**
- **Identification**
- **Quality**
- **Purity**
- **Stability**

Nanomaterial

- Microscopy (AFM, TEM, SEM)
- Light scattering (Static, Dynamic)
- SEC, FFF
- Electrophoresis (CE, PAGE)
- Zeta sizer
- Fluorimetry



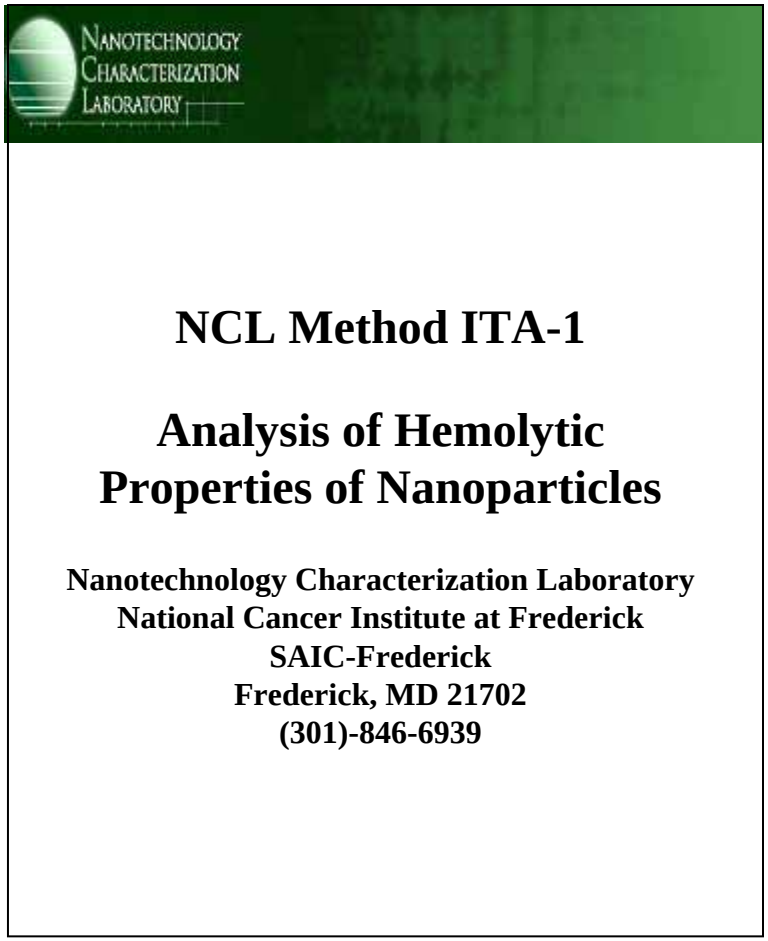
Same parameters – different/additional characterization methods

http://ncl.cancer.gov/working_assay-cascade.asp

In Vitro Cascade

- **Sterility**
  - Bacterial/Viral/Mycoplasma
  - Endotoxin
- **Cell Uptake/Distribution**
  - Cell Binding/Internalization
  - Targeting
- **Blood Contact Properties**
  - Plasma Protein Binding
  - Hemolysis
  - Platelet Aggregation
  - Coagulation
  - Complement Activation
  - CFU-GM
  - Leukocyte Proliferation
  - Macrophage/Neutrophil Function
  - Cytotoxic Activity of NK Cells
- **Toxicity**
  - Phase I/II Enzyme Induction/Suppression
  - Oxidative Stress
  - Cytotoxicity (necrosis)
  - Cytotoxicity (apoptosis)

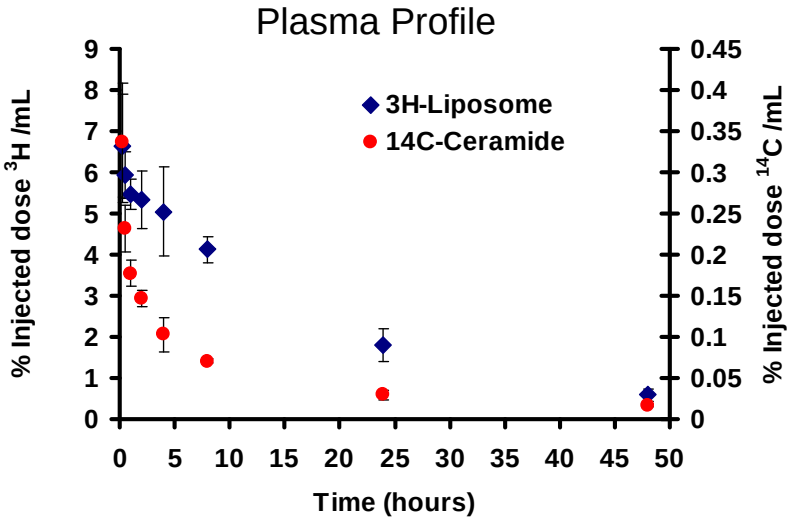
http://ncl.cancer.gov/working_assay-cascade.asp



In Vivo Cascade

- **Initial Disposition Study**
  - Tissue Distribution
  - Clearance
  - Half-life
- **Dose-Range Finding Toxicity**
  - Blood Chemistry
  - Hematology
  - Histopathology
  - Gross Pathology
- **Efficacy**
  - Therapeutic
  - Imaging
  - Transgenic and xenograft models

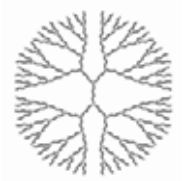
Dual Radiolabels



http://ncl.cancer.gov/working_assay-cascade.asp

Portfolio of Nanomaterials

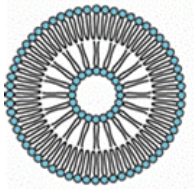
- 200 nanomaterials characterized; more than 65 collaborators, >90% extramural
- 3 nanomaterials now in clinical trials; more projected for 2010
- NCL annual budget of $3M supports work that would exceed $14M if conducted at a CRO



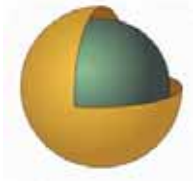
Dendrimers

Fullerenes

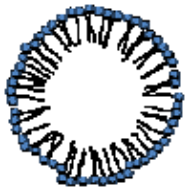
Quantum Dots



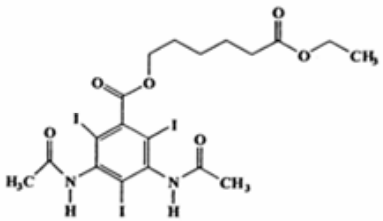
Liposomes



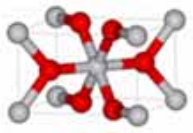
Gold nanoshells



Nanoemulsions



Nanocrystals



TiO_2

NCL Extramural Collaborators

Standards Development

- First voluntary consensus standards for biocompatibility-testing of nanomaterials intended for medical applications
  - E2524 (hemolysis), E2525 (CFU-GM inhibition), E2526 (kidney and liver cytotox)

- NCI supported the production of NIST's colloidal gold RM
  - Gold selected for calibration and biocompatibility
  - 10nm, 30nm, and 60 nm diameters

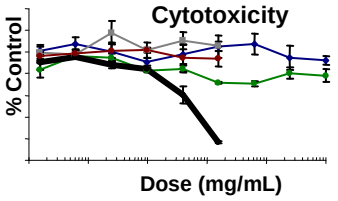
Standard Reference Materials

Standard Methods

Interlaboratory Comparison

ASTM ILS 166, Fall 2008

Lessons Learned: Biocompatibility



Nanoparticle Biocompatibility

(+)

Cytotoxicity
(Surface Reactivity)

Hi

RES
Recognition

Zeta Potential

0

Renal Clearance

Biliary Clearance ?

Hydrophobicity

(EPR Effect)

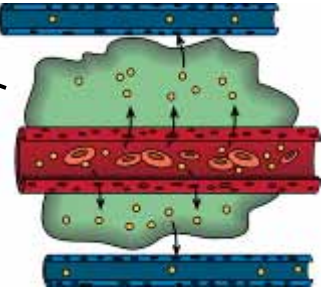
(–)

Low

1 nm

220 nm

Size
(Rigid Core)



McNeil, (2009), Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology, 1:264-271.

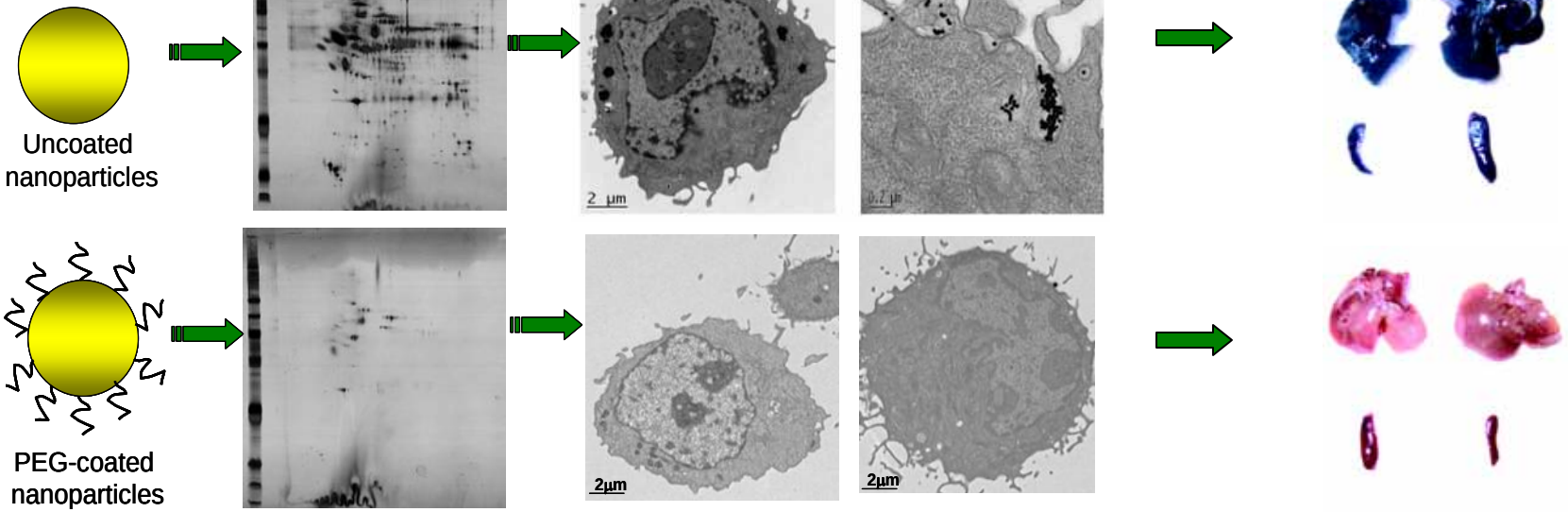
In Vitro to *In Vivo* Correlation

in vitro

in vivo

Protein analysis by 2D PAGE

TEM analysis of particles uptake by macrophages



Dobrovolskaia et al. (2008) Mol.Pharm., 5:487-495

Paciotti J. et al (2004) Drug Delivery,11:169-183

Binding of plasma proteins influences particle stability, biodistribution and clearance.

Lessons Learned

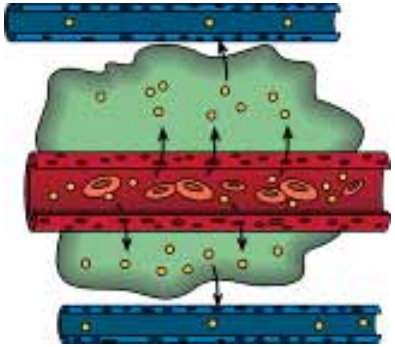
Biocompatibility

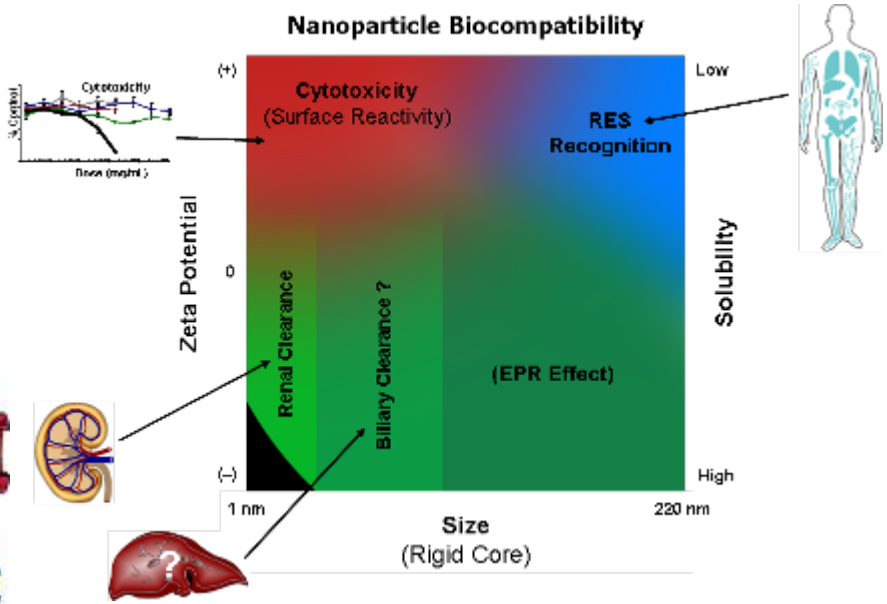
+

Tumor Accumulation

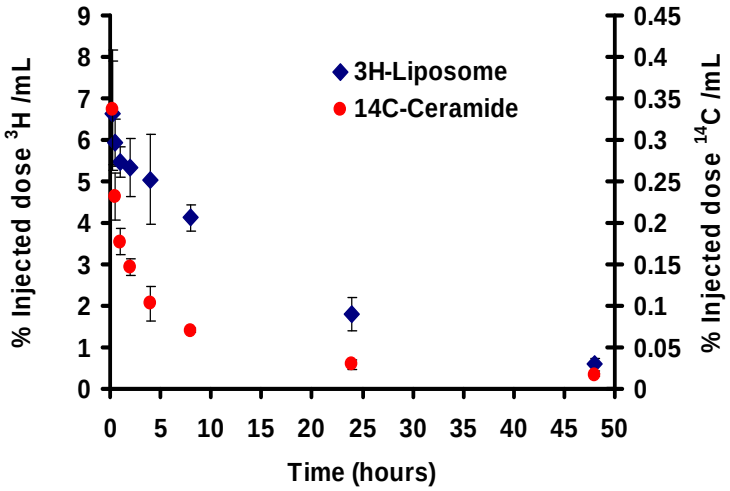
+

Nanoparticle Stability/ Controlled Release





Efficacy/Toxicity



Lessons Learned - Science

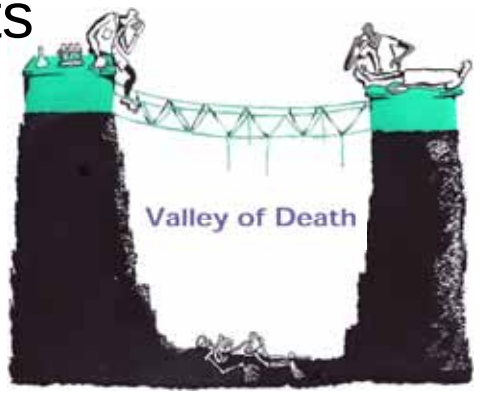
- Small changes in parameters can dramatically influence biocompatibility
  - Surface Charge
  - Size
  - Hydrophobicity/solubility
- Importance of *in vivo* stability
- Importance of characterization
  - Batch to batch variability
  - Physical parameters greatly affect ADME/Tox

Every particle is unique!

Lessons Learned - Programmatics

- Positives
  - Gov collaboration
  - FDA interactions
  - Three NPs in clinical trials

- Hurdles
  - Intellectual Property (IP)
  - Cultures: Gov, Industry, Academia
  - NCL's role, as perceived by applicants
  - Small molecule mentality

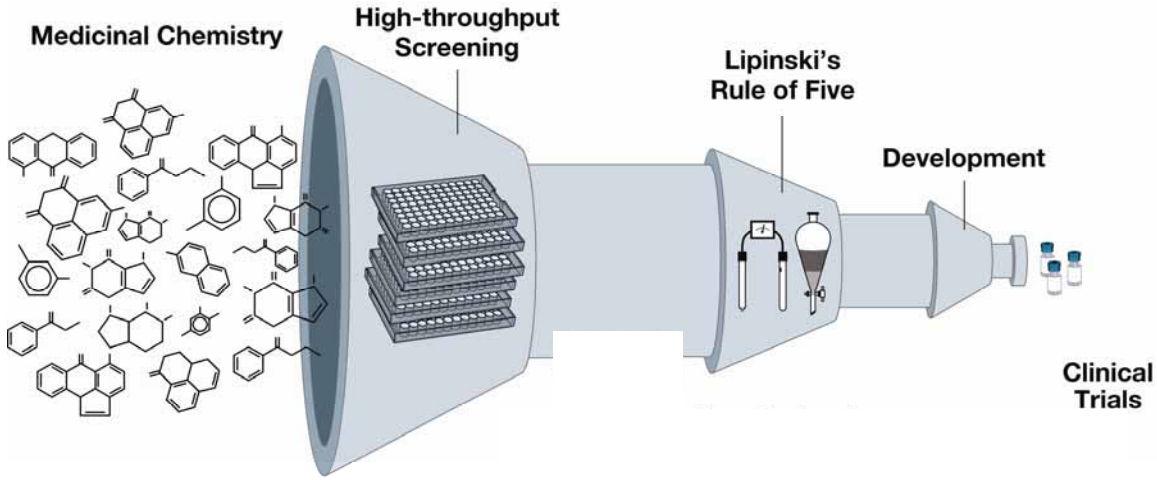


Nature 453, 840-842 (2008)

Future Directions

- In FY2010, expanding collaborations with other agencies (NCTR, NIEHS) to facilitate risk assessment and regulatory studies

- Reformulation of discontinued/failed drugs
  - Collaborate with Pharma and nanotech companies to identify candidates discontinued due to unfavorable pharmacokinetics (e.g. $t_{1/2}$ or distribution)



Future Directions

- Advanced Technology Research Facility (ATRF)
  - NCL will be relocating in 2012.

Progress…

NANOTECHNOLOGY CHARACTERIZATION LABORATORY

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CYTIMMUNE SCIENCES INC

Phase 1 Clinical Trials Complete in 2008

"The NCL has been and continues to be a critical component in CytImmune Sciences, Inc.'s efforts in bringing its first nanomedicine, CYT-6091 (Aurimune®) into the cancer therapeutic marketplace."

- Lawrence Tamarkin
President & CEO
CytImmune Sciences, Inc.

AZAYA THERAPEUTICS™

IND 2009

"NCL has been an essential resource for us in moving our therapy to the clinic, both through their insight as to the types of information needed to better understand the properties of our materials, as well as conducting specific studies to answer questions posed by FDA. "

- J. Donald Payne
President & CEO
Nanospectra Biosciences, Inc.

Nanospectra

IDE 2008

Acknowledgements

NCL

Anil K. Patri, Ph.D.
Marina A. Dobrovolskaia, Ph.D.
Pavan Adiseshaiah, Ph.D.
Jiwen Zheng, Ph.D.
Rachael M. Crist, Ph.D.
Chris B. McLeland, B.S.,M.B.A
Sonny Man, M.S.
Barry W. Neun, B.S.
David Parmiter, B.A.
Lesley Graham, M.S.
Martin Fritts, Ph.D.
Stephan T. Stern, Ph.D.
Jeffrey D. Clogston, Ph.D.
Jennifer B. Hall, Ph.D.
Sarah Skoczen, M.S.
Matthew Hansen, M.S.
Tim M. Potter, B.S.
Jamie Rodriguez, B.S.
Ruyin Shi, M.S.

Funded by NCI Contracts N01-CO-12400 and HHSN261200800001E

Contract HHSN261200800001E – Funded by the National Cancer Institute

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