



NCI **Alliance** for
Nanotechnology
in Cancer

Nanotechnology Characterization Lab (NCL) as a National Program

Scott McNeil, NCL Director
Presented to FNL Advisory Committee
February 3, 2015

<http://ncl.cancer.gov>



**NATIONAL[®]
CANCER
INSTITUTE**

**Frederick
National
Laboratory**
for Cancer Research

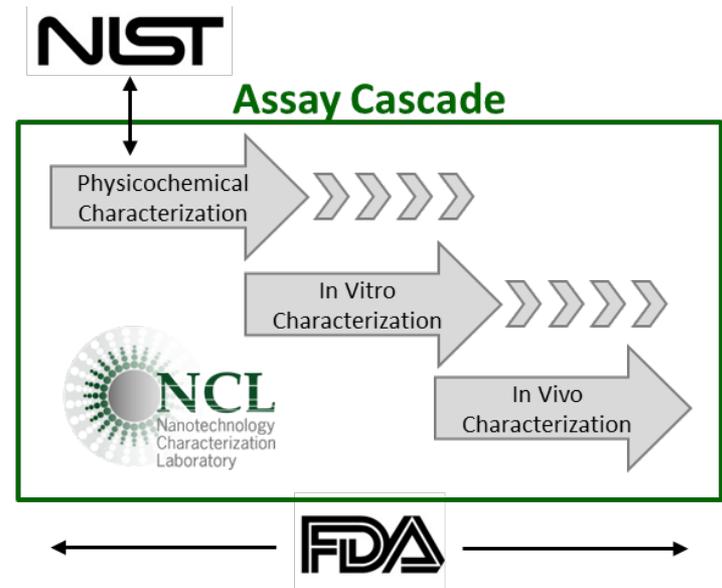
 **leidos**
Leidos Biomedical Research, Inc.

Previous FNLAC (NFAC) Briefings

- Jan. 2012, Introduction
 - NCL overview - P. Grodzinski
- Sept. 2012, Follow-up
 - NCL - P. Grodzinski & S. McNeil
- Sept. 2014, Update on FNLCR programs
 - NCL as a National Mission - D. Heimbrook

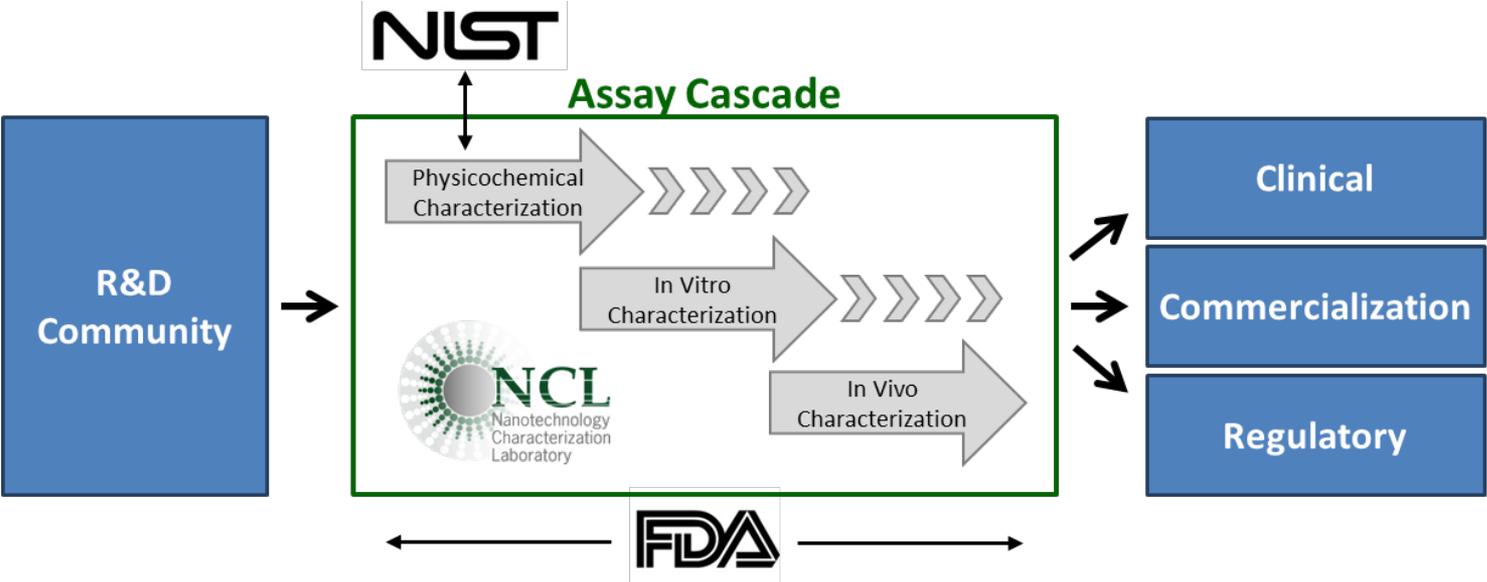
Today

- NCL evolution to present
 - Uniqueness; First 10 years
- Rationale for National Program
 - A synergistic effort that fills a need and would not happen otherwise
- Plan: resources, metrics, impact



**Seeking FNLAC Input and Vote of Support for
NCL as a National Program**

Historical NCL - Assay Cascade



- NCL provides independent verification of results → can help attract investment, de-risks products.
- Provides “pharmaceutical mentorship” for materials scientists and engineers.
- Repeat player with FDA: NCL provides submitters a preview of what FDA may be concerned with based on past experience.



Continue to Provide Assay Cascade Resource

- Provides “pharmaceutical mentorship” for materials scientists and engineers



Reformulation & cGMP

- Collaborations with Pharma, CMOs & industry consortia



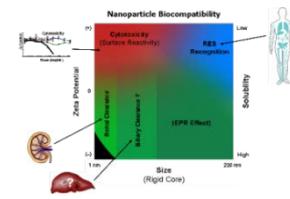
Nanomaterials

- Other indications, EHS, etc.



Metrology & New Methods

- Working with instrument manufacturers



Basic Research & Grand Challenges

- Immunotox
- Active targeting



Informing Regulatory

- Equivalence testing for nanosimilars
- Addressing FDA’s scientific questions
- NBCDs



Transnational Collaboration

- EU-NCL

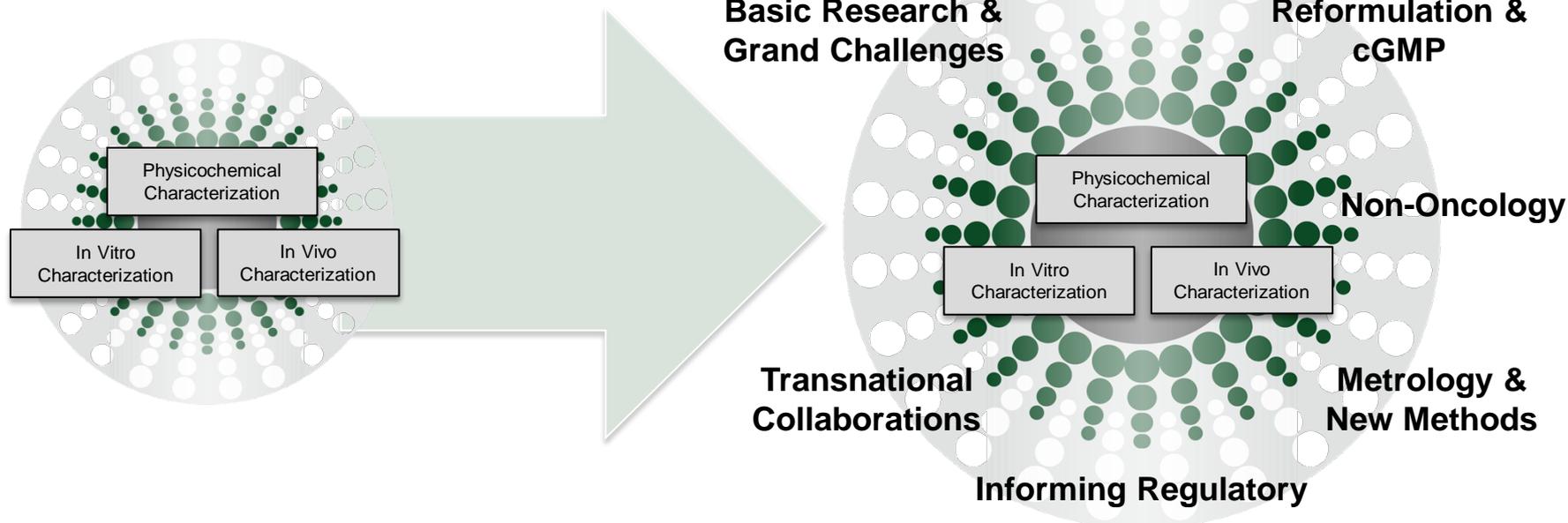


Why NCL as an FNL National Program?

- To meet the evolving needs of the nano community
- NCL is uniquely positioned to meet these needs

National Program

NCL 1st Ten Years



Leverages NCL's unique expertise to create a National Resource for nanomedicine.



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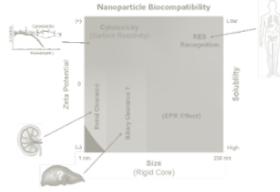
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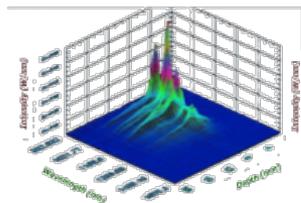
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Assay Cascade Outcomes

Physicochemical



In vitro

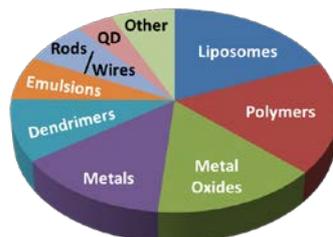
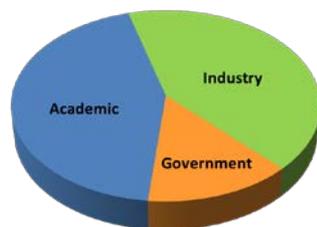


In vivo



- NCL testing is tailored to the platform properties, API, route of administration, and intended therapeutic outcome of the individual nanomedicine.
- **NCL testing links physicochemical properties to biological outcomes.**
- NCL has characterized over 300 different nanomaterials and a wide range of platforms. Ten collaborators with products in clinical trials.
- NCL has an average of 15 active collaborations at any given time and characterizes an average of 75 samples each year.

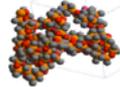
Source and Types of Samples



Dendrimers



Liposomes



Polymers



Nanoemulsions



Gold Nanorods



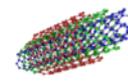
Quantum Dots



Core-Shell



Nanocrystals
(e.g. TiO₂)



Carbon
Nanotubes



Fullerenes



Gold
Colloids



Silver
Colloids

NCL is the only lab evaluating the wide variety of platforms used in nanomedicine. Ten years of providing NCL Assay Cascade testing has given NCL expertise that is unique in the world.

NCL Extramural Collaborators

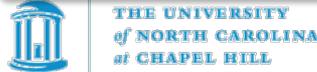
In clinical trials



NCI Alliance for Nanotechnology in Cancer



PENNSYLVANIA STATE UNIVERSITY





Continue to Provide Assay Cascade Resource

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Reformulation & cGMP

- Collaborations with Pharma, CMOs & industry consortia



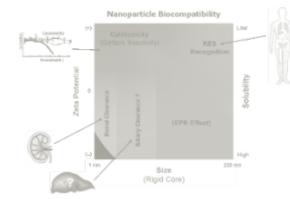
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Metrology & New Methods

- Working with instrument manufacturers



Basic Research & Grand Challenges

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Informing Regulatory

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Transnational Collaboration

- EU-NCL

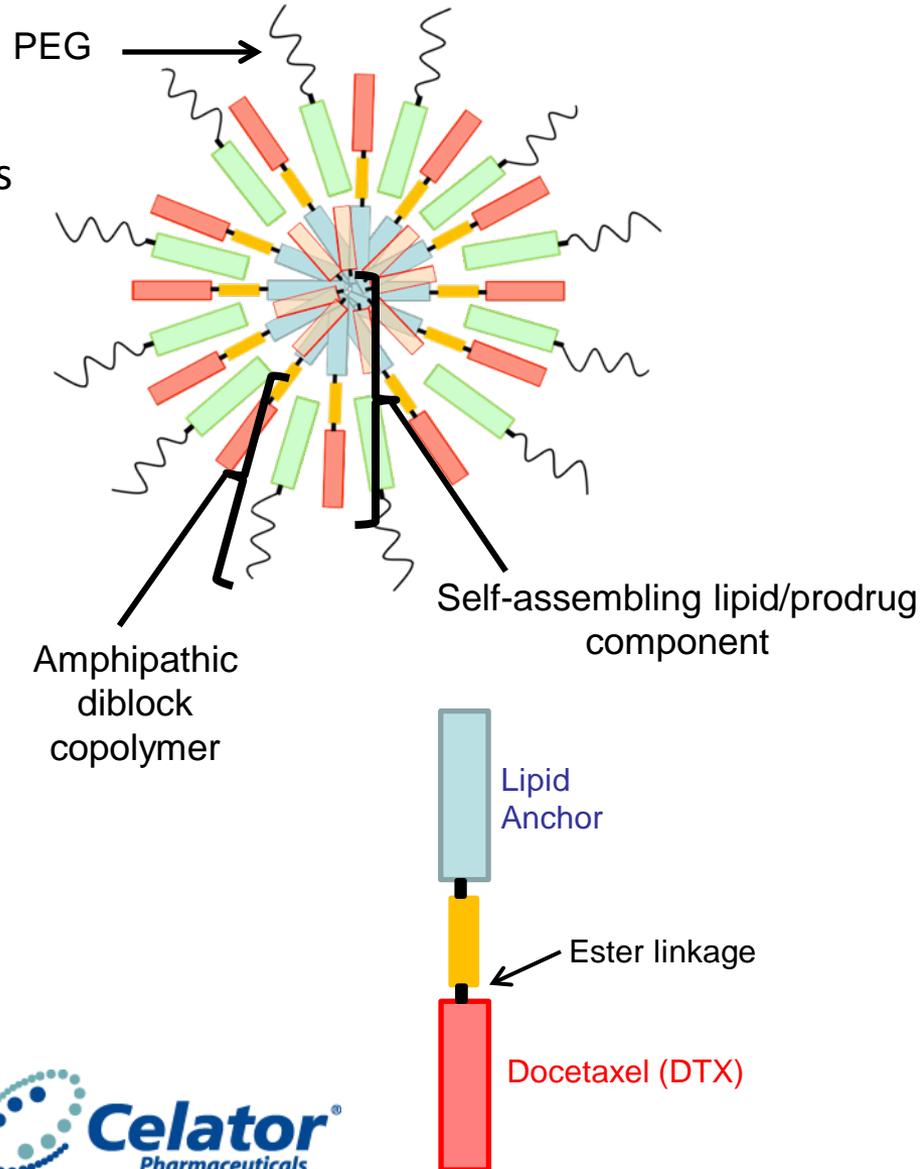


Nanotech Reformulation can:

- Increase the solubility of hydrophobic drugs
- Alter the PK profile
- Reduce drug toxicity

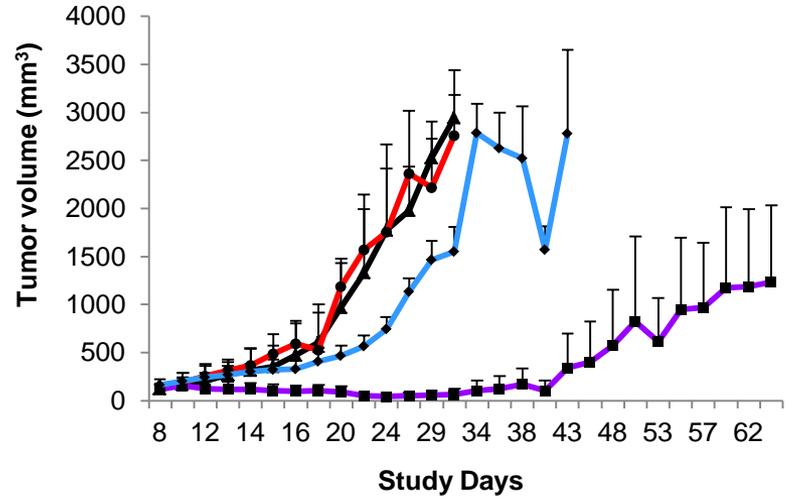
Case Study: Nanomicellar Docetaxel Prodrug

- Nanoparticle targets tumor by EPR, prodrug is released and hydrolyzed to DTX
- In addition to EPR, are there additional advantages for systemic controlled release formulations?



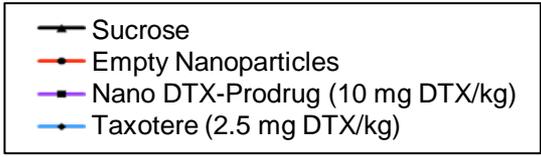
Case Study: Nanomicellar Docetaxel Prodrug

Tumor Volume

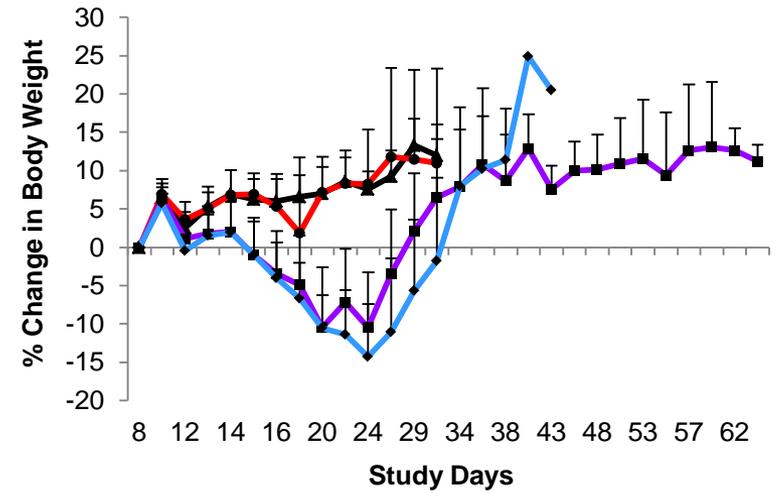


Q2dx5 MTD

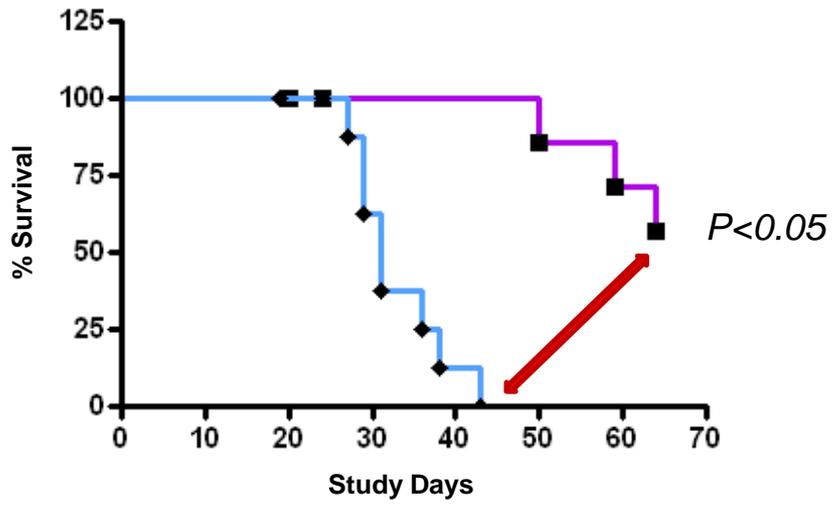
Nano DTX-Prodrug: 10 mg DTX/kg
Taxotere: 2.5 mg DTX/kg
Colon Cancer Xenograft



% Change in Body Weight



Animal Survival



Improved therapeutic index!

Nanoformulations have complex, multi-step synthesis processes:

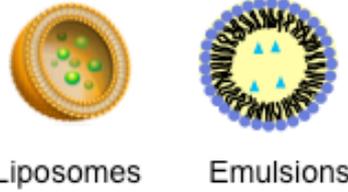
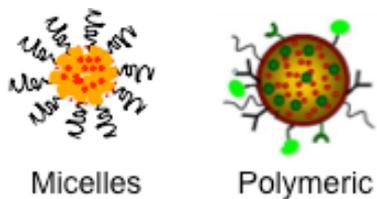
- Require in-process characterization at each step in scale-up
- Are complex mixtures of closely related structures; not easy to eliminate batch-to-batch variability
- FDA increasingly asking for specialized testing: orthogonal characterization, drug release, bioassays to demonstrate equivalence
- Few Contract Manufacturing Organizations (CMOs) with capabilities for cGMP manufacturing of nanomedicines
- Common for nanomed cGMP lots to fail to meet specs or fail efficacy testing



Issues with scale up and cGMP remain a challenge for nanomedicine industry.

Current NCL

- Uniquely nuanced expertise about what works and doesn't work for nanomedicines
- Collaborations with USAMRIID, AstraZeneca



National Program

- Meet demand from Pharma and Gov Agencies for NCL reformulation collaborations
- Production for larger portfolio of nanomedicines
- Collaborations with CMOs and industry consortia, cGMP capabilities to support scale-up efforts
- Address previously disqualifying toxicity or missed metric.





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Reformulation & cGMP

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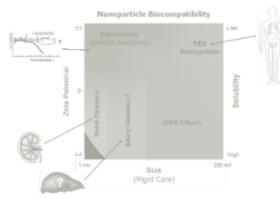
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Transnational Collaboration

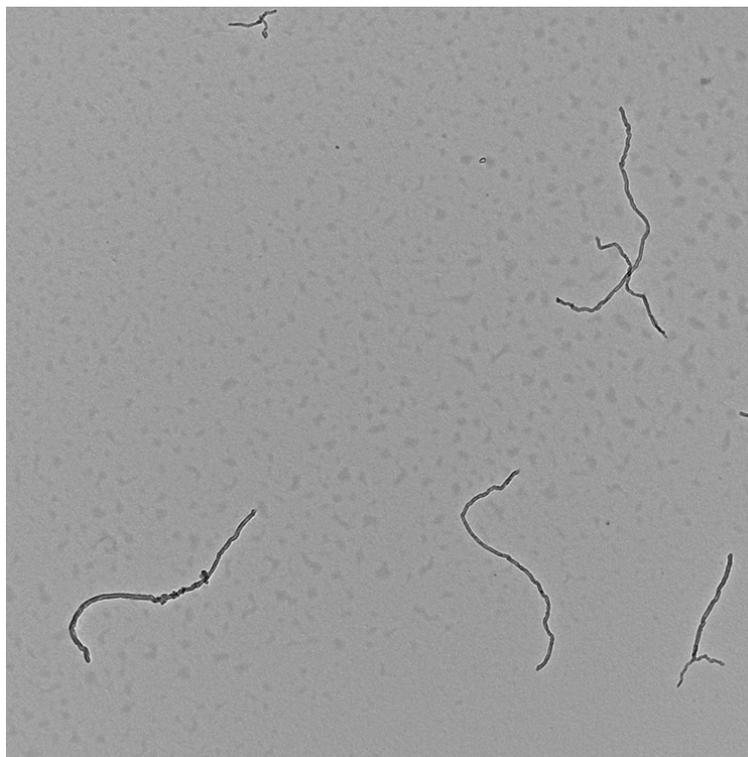
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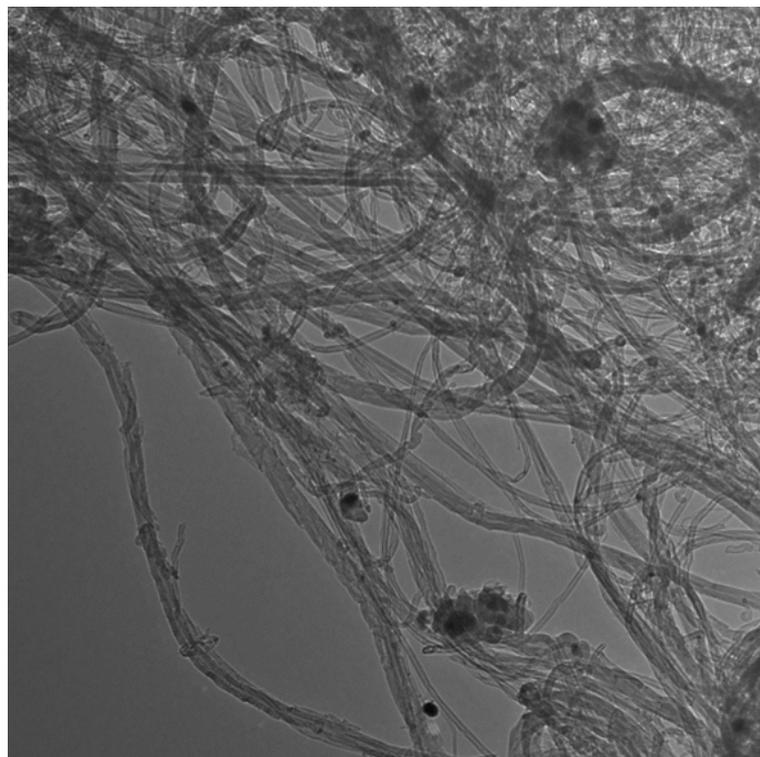


NCL conducted physicochemical characterization of nanomaterials for NIEHS's U19 program.

CNTs What's Often Shown:



CNTs In Reality:



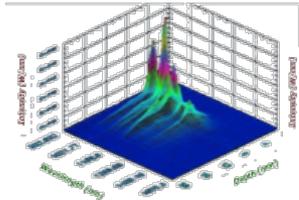
CNTs exist in a variety of sizes, shapes, and agglomeration states.

NCL Assay Cascade is relevant to nanomaterials for non-oncology applications

Current NCL

- NCL physicochemical and in vitro characterization methods are applicable to other nanomaterials
 - E.g. EHS and non-cancer nanomedicines
- Funded collaborations for characterization of non-cancer nanomaterials for FDA and NIEHS

Physicochemical

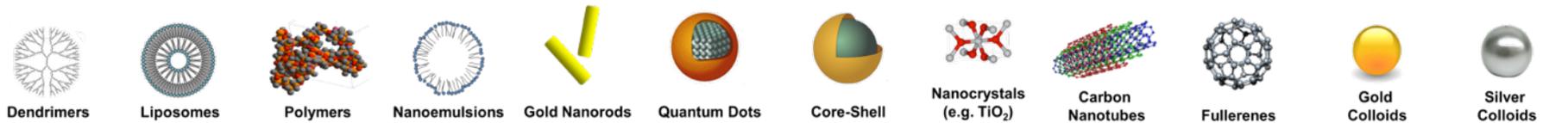


In vitro



National Program

- Meet demand from industry and Gov Agencies for characterization
- Leverage NCL characterization resources in support of all NIH/HHS efforts in nanomedicine and EHS





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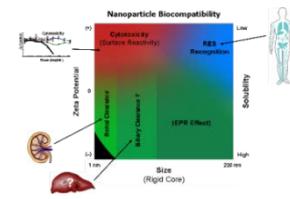
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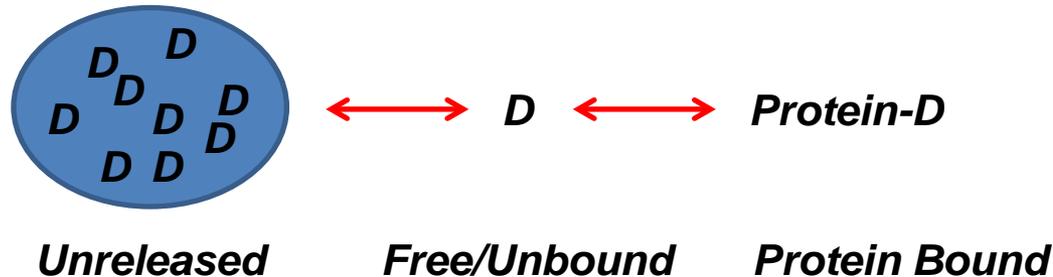


Transnational Collaboration

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D = Biologically Active Substance



- Multiple drug fractions.
- Nano-formulation can affect drug-protein interactions.
- Unbound drug can be in equilibrium with both the formulation components and protein
 - Taxol[®], a cremophor micelle formulation, is an example.

Bioequivalence studies require evaluation of drug release and unencapsulated drug fraction.

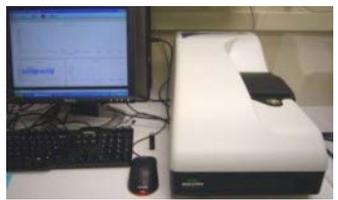
Current NCL

- NCL has developed novel assays for physicochemical characterization, immunology, and to assess nanoparticle stability and drug release



National Program

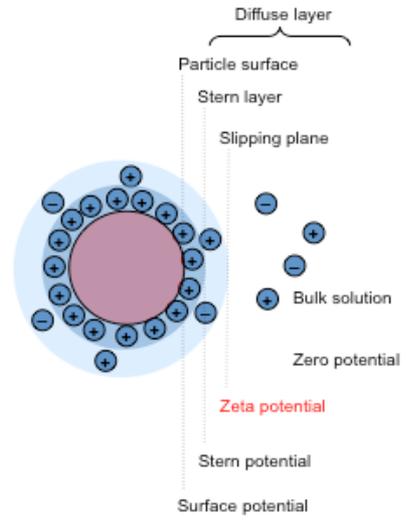
- Collaborations with instrument manufacturers
- Develop drug release methods with Pharma to support clinical trials and bioequivalence
- Collaborations with FDA to fill gaps/better inform regulatory process



DLS



FFF





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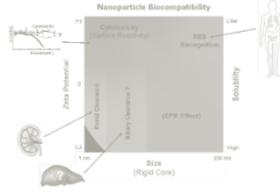
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Understand role of nanoparticle physicochemical properties on immunological reactions

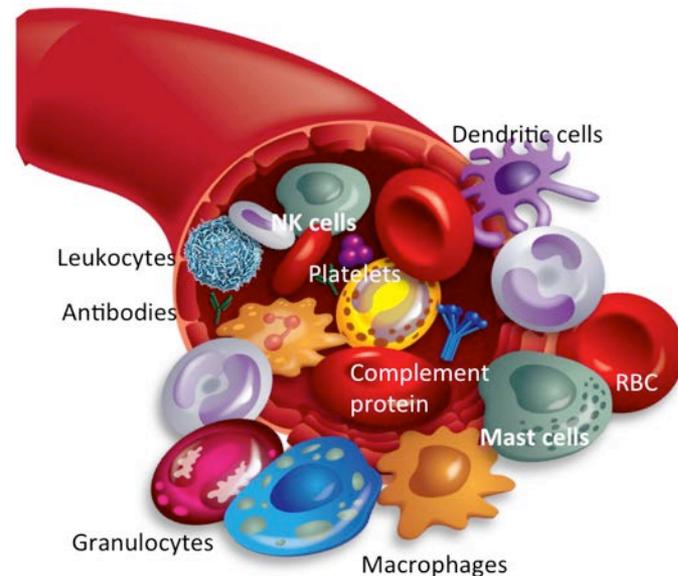
Immunotoxicity of nanoformulations vs. traditional formulations

Hematology

- Hemolysis
- Thrombogenicity: platelet aggregation and leukocyte procoagulant activity (PCA)
- Activation of complement

Immune Cell Function

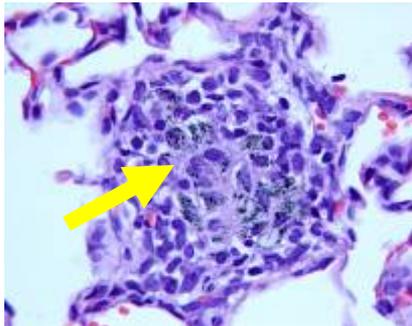
- Opsonization and MPS uptake
- Inflammatory cytokines



14-day ADME-Tox Study in Rats

Batch 1

Extensive pigmentation in liver, spleen, lungs, ovaries, muzzles. Treatment-related granulomatous lesions in lungs.



**Pyogranulomatous Inflammation-
Lung- H&E-40x**

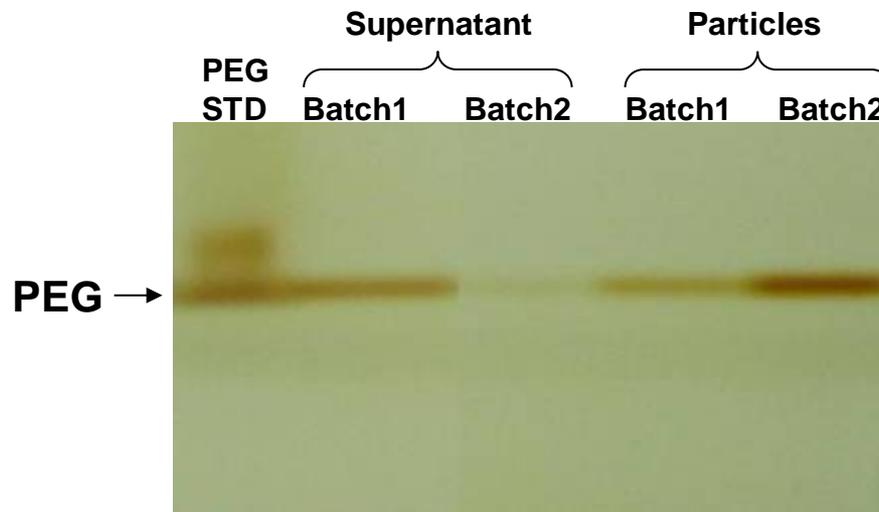
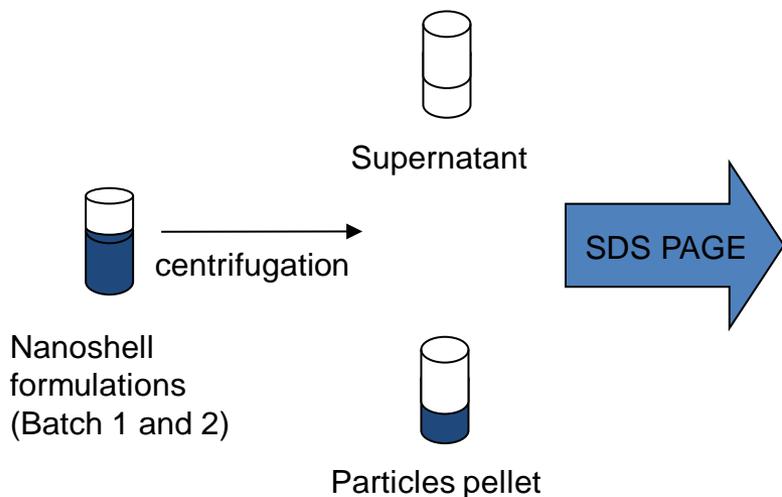
Batch 2

Much less pigmentation. Few, statistically insignificant, mild lung lesions.



In tox studies, 1st batch caused extensive lung lesions, 2nd batch was largely benign.

Difference in PEG Coatings

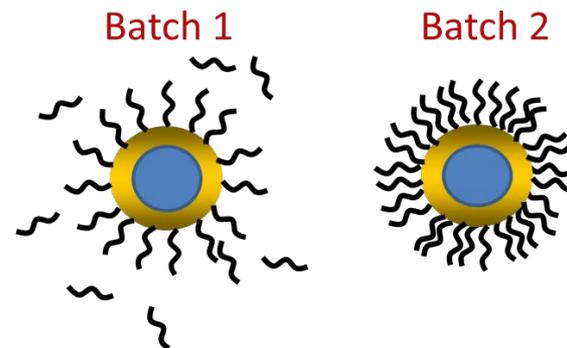


Barium Iodine Gel Staining

PEG was dissociating from the particles over time, ending up in solution.

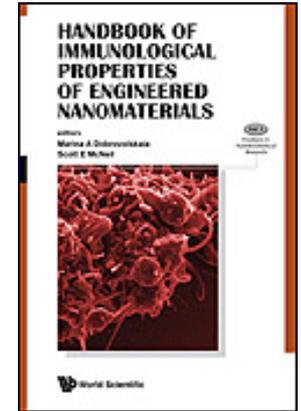
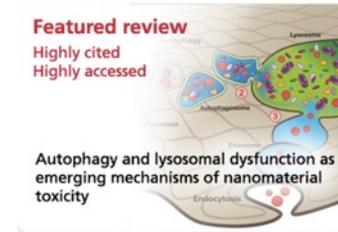
This difference in coatings was subtle enough not to be detected by routine PCC...but resulted in aggregation *in vivo*

Physicochemical Equivalence ≠ Bioequivalence
Relevant PCC was not known *a priori*



Current NCL

- NCL has over 100 publications; NCL scientists are internationally recognized experts
- NCL basic research and SAR studies on trends have informed the nanomedicine community and influenced the field



National Program

- NCL would serve as a Hub for nanomedicine research community, connect academics, industry, and FDA
- Host meetings, web-based collaboratory, working groups to identify “Grand Challenges”
- Leverage NCL resources to solve scientific problems identified by external community as impeding the field, preventing translation





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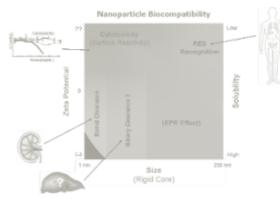
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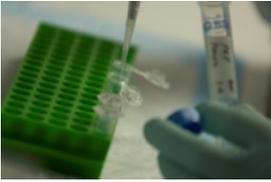


Transnational Collaboration

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- NCL allows FDA to preview what's in pipeline for nanotech INDs/IDEs.
- NCL is trusted source for preclinical data on nanomaterials.
- Scientific collaborations with FDA to address specific concerns for nanotech:
 - Immunological reactions to nanomaterials, dermal penetration of nanomaterials in sunscreens and cosmetics, endotoxin, methods of sterilization for devices.
- FDA provides input on NCL's assay cascade and is represented on NCL's scientific oversight committee.
- NCL participates in FDA public meetings on topics related to nanomedicine.



CDER
CBER
CDRH
CFSAN

Informing Regulatory: “Nanosimilars” ≠ Generics, Biosimilars

API Identity is Known

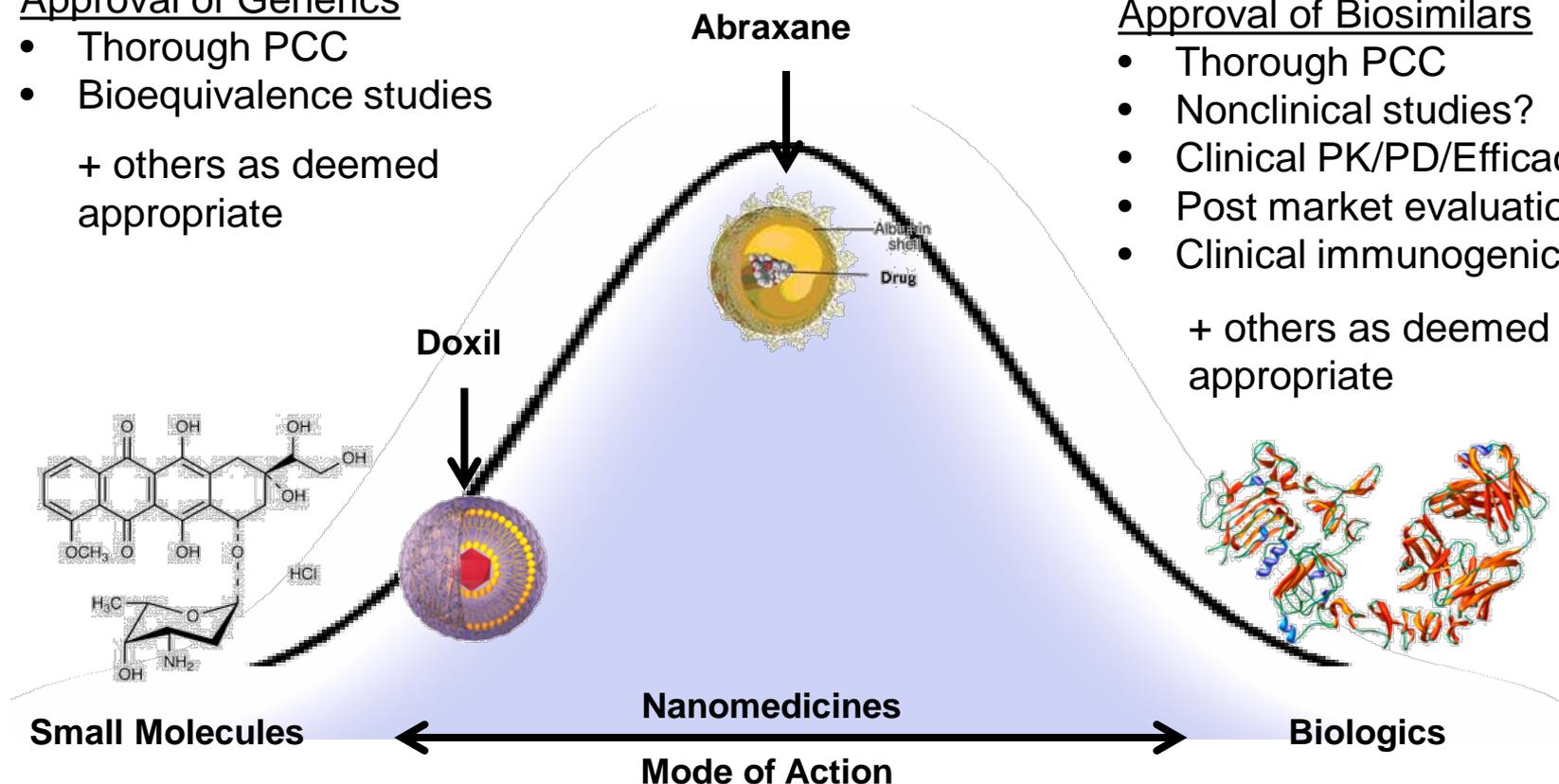
Common Requirements for Approval of Generics

- Thorough PCC
 - Bioequivalence studies
- + others as deemed appropriate

API Identity is a Complex Mixture

Common Requirements for Approval of Biosimilars

- Thorough PCC
 - Nonclinical studies?
 - Clinical PK/PD/Efficacy
 - Post market evaluation
 - Clinical immunogenicity
- + others as deemed appropriate



Current NCL

- Quarterly interactions (visits, working groups) with FDA to maintain collaboration
- Collaborations with FDA for specific scientific areas conducted through IAAs

National Program

- Collaborations with FDA to fill gaps/better inform regulatory process: methods development, basic research and grand challenges
- Interactions with international regulatory bodies: EMA, Health Canada, etc.
- Addressing regulatory concerns facilitates commercialization
- Need mechanism for NCL to submit research proposals to FDA and other Gov Agencies





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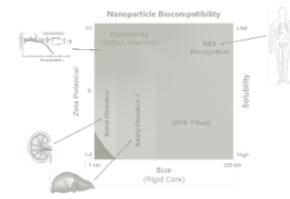
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EC Funding “mirror lab” to NCL in Europe

- Four year Research Infrastructure grant under Horizon 2020
- Consortia of 8 academic, industry, and government labs distributed throughout EU



US-NCL Funded to Leverage Historical Knowledge

- Reduce risk of adverse events
- Leverage scale up resources
- United effort will expanded visibility of nanomedicine to users, Pharma, VC, R&D community, and regulatory agencies (EMA & FDA)



US-EU Collaboration to Facilitate Regulatory Coordination

- By working with EMA, US-NCL and EU-NCL can inform EU and FDA regulatory policy for nanomedicines → coordination
- Complementary regulatory framework decreases perceived regulatory hurdles and increases investment

EU-NCL now funded by the EC for 2015.



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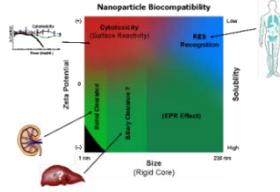
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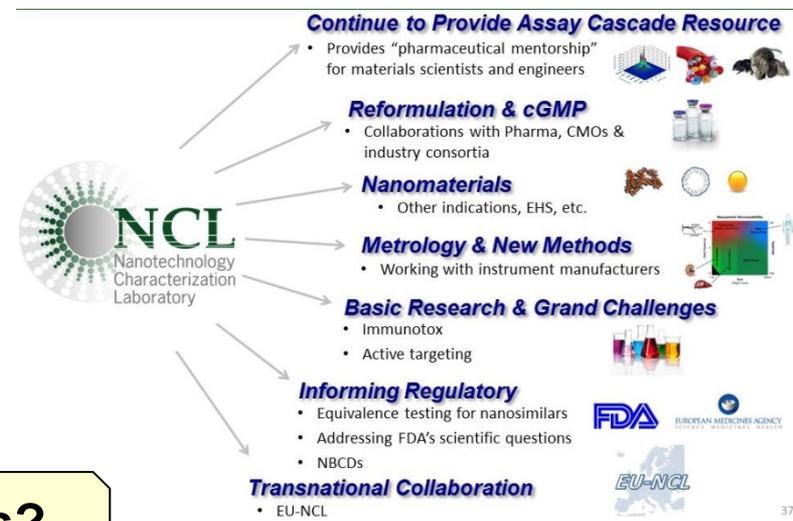


Recommended Resources

- NCL National Mission could be supported with an additional \$1.5-2MM per year.
 - 8 FTEs, 3 postdocs, capital equipment
 - These funds expected to be offset by industry in year 3
- GMP scale-up facility for approximately \$15MM.
 - Milligram to gram-level scale-up
 - Address the phase I-II level
 - Funding of infrastructure, retooling of existing facilities
- Anticipate extensive collaboration and financial support from the extramural community (through e.g., CRADAs, interagency agreements, and grants).

Significance & Impact

- Utilizes and recognizes NCL as a unique international resource.
- Clinical translation of promising nanomedicines to clinics and patients.
- Global resource for nanomedicine and nanomaterials.
- Successful reformulation of APIs, new methods development, informed & harmonized regulatory agencies, new grand challenges in nanomedicine research...
- Basic research and publications.
- Projects FNLCR's impact.



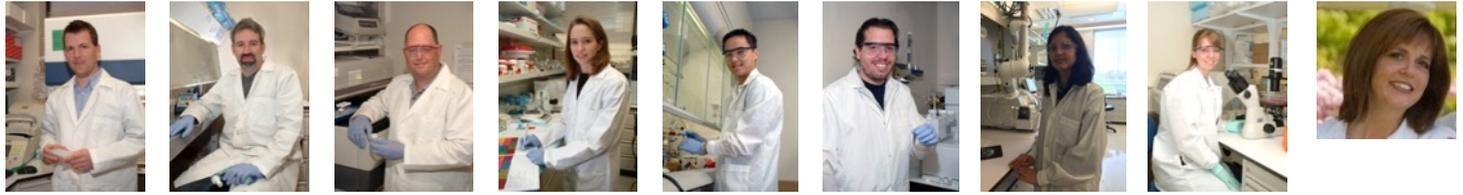
Does the FNLCAC support these efforts?

Acknowledgements

Nanotechnology Characterization Lab



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