NIEHS Nanotechnology Research Update: Current Activities and Future Plans

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ERTB/DERT/NIEHS
Mission: Reduce the burden of human illness and disability by understanding how the environment influences the development and progression of human disease.
NIEHS Nanotechnology Research program

- Division of Extramural Research and Training
- Nano EHS
- Nanotechnology applications
  - Sensors (environmental)
  - Personal monitoring (point of contact)
- Investigator-initiated research
- Request for Applications (RFA)

- Division of National Toxicology Program
  - Contract research
  - Peer reviewed research reports
- Division of Intramural Research
- Laboratory and clinical research
NNI Nano EHS Research Strategy: Focused areas

- Human Health
- Human Exposure Assessment
- Nanomaterial Measurement Infrastructure
- Environmental Effects
- Risk Assessment and Risk Management Methods
- Informatics and Modeling for Nano EHS Research
NIEHS Nano EHS Overarching Goals

- Gain fundamental understanding on the interactions between engineered nanomaterials (ENMs) – biology
  - Physicochemical characteristics

- Develop comprehensive toxicological data
  - Prioritize ENMs
    - Production, use, and physicochemical properties
    - Integrated approaches for hazard ranking

- Serve as reference data to address
  - Public health issues
  - Regulatory needs
ARRA Nano Grand Opportunity Consortium

Develop **reliable and reproducible methods** to assess biological response/toxicological endpoints for ENMs.

- Utilize ENMs with well defined physicochemical properties
- Develop **standardized protocols** and methods for ENM dispersal and characterization in cell culture media.
- *In vitro* and *in vivo* models that can reliably predict biological response and reproducible data across labs using well characterized ENMs
NIEHS Centers for Nanotechnology Health Implications Research (NCNHIR)

**Project #1: In Vitro**  
Understand basic ENM-biological interactions (molecular, cellular, organelle, organ level). Diverse cell phenotypes, representing portals of entry

**Project #2: In Vivo**  
Investigate how ENM PCPs influence physiological pathological outcomes in target/secondary organs; ADME, translocation across different organs

**Project #3: Risk Assessment Translation**  
Develop RA framework  
In Two phases:  
Phase1: conceptual framework  
Phase2: Collaborative/integrated

Consortium ENMs:  
Silver (20, 110; citrate, PVP)  
MWCNTs (3 AR)

33 ENMs, 18 sizes, 12 surface modifications  
Metals (27), carbonaceous (6), QDs (3)
NCNHIR Consortium Highlights

• In vitro studies using four silver ENMs indicated:
  – Cell-specificity in acute toxicity responses
  – Role of protein corona

• High throughput screening of metals and metal oxides clearly suggested:
  – Initiation of acute pulmonary inflammation
  – Susceptibility to pulmonary infection
High throughput screening

Cells

Dissolution

Multiplex Assays:
Cytokines
Chemokines

Reactive surface

CuO
ZnO

Fe$_2$O$_3$
Fe$_3$O$_4$
WO$_3$

CoO
Co$_3$O$_4$
Cr$_2$O$_3$
Mn$_2$O$_3$
Ni$_2$O$_3$

Al$_2$O$_3$, CeO$_2$,
Gd$_2$O$_3$, HfO$_2$,
In$_2$O$_3$, La$_2$O$_3$,
NiO, Sb$_2$O$_3$,
SiO$_2$, SnO$_2$,
TiO$_2$, Yb$_2$O$_3$,
Y$_2$O$_3$, ZrO$_2$

Nel’s group, UCLA
NCNHIR Consortium Highlights (2010-2015)

• In vitro studies using four silver ENMs indicated:
  – Cell-specificity in acute toxicity responses
  – Role of protein corona

• High throughput screening of metals and metal oxides clearly suggested:
  – Initiation of acute pulmonary inflammation
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• Studies with MWCNTs predicted fibrinogenic effects

• Species and strain specific acute pulmonary effects

• Acute vascular toxicity of Ag and MWCNTs

• Computational models (ADME, ISD3, BMD and QSAR)
Modeling Silver Nanoparticle Dissolution and Cell Dosimetry

• To understand the role of cellular dose in the differential toxicity of silver NP, the consortium extended a NP dosimetry model to treat dissolution and transport of particles and ions into cells (ISD3 Model).

• Capturing the time-dependent dissolution of silver NP and transport of silver into cells in culture allows improved dose response and enables extrapolation to animal models and humans.
Predictive Modeling: PBPK

Kinetics at cellular level

Routes of exposure

Physiology
Adult, Gestation, Lactation

Cellular toxicity & responses

Rat
Whole Body PBPK model

PD model

In vivo PD responses

Human in vitro data for PK & PD

Cross-species extrapolation

Cross-species validation: rat to mouse

Human PBPK/PD model for Risk Assessment

in vitro to in vivo extrapolation

incorporating life stages

Predictive Modeling: PBPK

in vitro to in vivo extrapolation

in vitro to in vivo extrapolation
C60 fullerenes Sub-chronic toxicity and immunotoxicity of Inhalation (50nm and 1um) and oral route- reports in prep

Nano silver sub-chronic studies and toxicokinetics (completed), reports in preparation

MWCNTs

- PCPs of 24 commercial CNTs (Levine et al 2014)
- Sub-chronic inhalation toxicity and clearance of a selected MWCNT completed and report is in preparation
  - 30 day functional immunotoxicity (inhalation) study will be initiated in spring 2015; NCNHIR consortium investigators will participate in these studies
  - Two-year chronic studies with MWCNTs to be initiated in late 2015
• Chemical Effects in Biological Systems database (CEBS) houses toxicological information of interest to health scientists.

• CEBS has a public and a private component.

• The public component houses over 9000 toxicological studies containing raw study data and metadata.

• Data from NTP Nano EHS and NCNHIR consortium efforts are being moved into CEBS and will be accessible to investigators/partners
  – Access to public as deemed fit

NanoCEBS Database

- DNTP/DIR Nano EHS
- NIEHS Grantees
- Federal Partners: US EPA- NHEERL FDA- NCTR NIST
- NCL Characterization Data
- NanoRegistry (NIBIB-NIEHS-NCI)
Research Gaps and Needs to Be Addressed…

• Expand knowledge base to gain insights into ENMs-biological interactions
  – Diverse classes of ENMs, material properties, biological endpoints
  – Emerging ENMs (2D-, and 3D)
  – Identified based on input from NNI (regulatory agencies) and state of science

• Comprehensive toxicity profiles
  – Molecular predictive toxicological approaches
  – Animal models using multiple routes of exposures
  – Chronic- and sub-chronic studies
  – Develop predictive biomarkers- target and secondary organ response
  – Identify common mechanism(s) of action across ENMs and routes of exposure
Moving forward - Basic Research

• Focused approach

• A limited set of ENMs
  – Pre-identified with input from regulatory agencies

• Two components
  – Materials resource core center
  – Research projects
    • Utilize diverse routes of exposure, target organs
    • Molecular, pathophysiological approaches for comprehensive toxicity profile(s)

• Form consortium
  – Annual meetings
  – Opportunities for collaborative efforts
Future Plans - Exposure Assessment

- Support development of tools for measurement and monitoring ENMs and Nanoenabled products

- Detection
  - Particle number, size, surface area

- Quantification and speciation
  - Real-time and archived samples
  - Metals, metal oxides, CNTs

- Spatial and temporal distribution

- Discrimination from ambient combustion generated nanoparticles
Opportunities for Collaborations

- Mechanisms for sharing materials
- Inclusion of additional experiments
- Specific data needs of regulatory agencies
- Promote partnership with international collaborators
- Participation at consortium annual meetings
- External advisory committee
- Access to CEBS-Nano
Thank You