NanoHealth Enterprise

NanoHealth Enterprise Coordination Meeting
Sponsored by the National Institute of Environmental Health Sciences
National Institute of Biomedical Imaging and Bioengineering
Bethesda, Maryland • January 16-17, 2008

Day One

7:30 **Breakfast and Registration**

8:30 **Welcome and Introduction**
– *Sam Wilson, Acting Director, NIEHS*
– *Belinda Seto, Deputy Director, NIBIB*

8:45 **Overview of the Meeting Program**
– *William Heetderks*

9:00 **Focusing the Science**
- Review of the critical questions to understand nanobiointeractions - *Sally Tinkle*
- Review of existing nanomaterials characterization tools/methods/protocols for investigating nanobiointeractions
– *Marty Fritts*

10:00 **Break**

10:15 **Perspectives on a Public-Private Partnership (PPP): *What's the view from your sector?***
– *Annette Kolodzie, Skip Rung*
- What could a NanoHealth PPP do that couldn't be accomplished some other way?
- What would compel our organization to participate in the PPP (What benefit must you get)?
- What expertise or resources would our organization bring to the PPP in order to get the expected benefit?
- What obstacles do I see that would hinder the PPP from being productive?

Sector Presentors:

Large/Medium Industries
- *Keith McIver*, Boeing
- *Michele Ostraat*, RTI/NOSH Consortium
- *Annette Kolodzie*, FEI
- Pharma representative (tentative)

Small/Startup Industries
- *Sean Murdock*, Nano Business Alliance
- *Charles Grause*, Luna Innovations

Academic Consortia
- *Vicki Colvin*, International Council on Nanotechnology (ICON)
- *Kang Wang*, California Nanosystems Institute (CNSI)
- *David Pui*, U. of Minnesota

Public Health Advocacy
- *Andrew Maynard*, Woodrow Wilson Center

Federal Agencies
- Materials–*Eric Steel*, NIST
- Research–*Nora Savage*, EPA
- Regulatory–*Rick Canady*, FDA

12:00 **Lunch**

1:00 **Ground Rules for Working with NIH**
– *Barbara Mittleman*

1:10 **PPP Concepts and Strategies from the FNIH Perspective**
– *Daniel Carucci*

1:25 **Breakout Dialogue #1: *Identifying participant and cross-sector requirements for building the NanoHealth Enterprise***
- Charge to the breakout groups
– *Skip Rung*

3:15 **Break and Report Editing**

4:00 **Group Reports and Discussion**
– *Annette Kolodzie*

5:00 **Day One Wrap-up: *Identifying breakout topics for Day Two***
– *Sally Tinkle, William Heetderks*

5:15 **Ad Hoc Planning Members and Moderators Meet**

Day Two

8:30 **Recap of Day One**
– *Sally Tinkle, William Heetderks*

8:45 **Breakout Dialogue #2: *Identifying the scientific projects we can do better together***
- Charge to the breakout groups
– *Michele Ostraat, Kang Wang*

10:15 **Break and Report Editing**

10:45 **Group Reports and Discussion**
– *Steve Hillenius*

11:15 **Summary: *What do you need to take back to your decision makers to engage them in building the NanoHealth Enterprise?***
– *Barbara Mittleman*

11:30 **Wrap-up and Next Steps**
– *Sally Tinkle, William Heetderks*

12:00 **Adjourn**

NIEHS National Institute of Environmental Health Sciences

NIBIB

NanoHealth
Enterprise

NanoHealth Enterprise Initiative

Engineered Nanomaterials Research and Training

Executive Summary

The properties that emerge at the nanoscale—size, surface-area-to-mass ratio, shape, crystal structure, surface chemistry, and surface defects—elicit electrical, optical, magnetic, and biological properties that enable novel applications in medical, industrial, and consumer products. The same unique chemical and physical properties that make engineered nanomaterials (ENM) so potentially useful also make their interactions with biological systems difficult to anticipate and critically important to explore.

The NIH proposes a broad-based program that would employ state-of-the-art technologies in research to examine the fundamental physicochemical interactions of ENM with biological systems at the molecular, cellular, and organ level. To support and promote this investigative work, an informatics framework to identify cross-cutting design principles, as well as training for the next generation of nanotechnology scientists are proposed.

Framework of the NanoHealth Enterprise

The NanoHealth Enterprise would comprise an integrated, interdisciplinary program that draws upon the expertise and interests of the NIH institutes and centers, in partnership with private industry, to address critical research needs for the safe development of nanoscale materials and devices.

- **Materials Science Research**—characterization of the physical and chemical properties of ENM in relevant biological systems;
- **Basic Biology Research**—determination of the relationship of nanoscale size and physicochemical properties to biological response at the cellular, molecular, and systemic levels;
- **Pathobiology Research**—investigation of the relationship of nanoscale size and physicochemical properties to ENM-induced pathophysiologic endpoints and the development of disease;
- **Informatics**—a data-sharing framework to store and structure information on the potential environmental, health and safety risks of ENM's with data-mining, query, and search capabilities; and
- **Training**—education of scientists to work on cross-disciplinary and interdisciplinary nanotechnology research teams, and to develop research programs that integrate materials science, biology, and pathobiology research.

Prepared by the National Institute of Environmental Health Sciences, National Institutes of Health, and U.S. Department of Human Health Services.

NanoHealth Enterprise Initiative

Engineered nanomaterials (ENM), with their precise design and engineering attributes and novel physicochemical properties, represent a significant breakthrough in material design and development for medicine, industry, and consumer products. Global demand for ENM and nano-enabled devices is expected to exceed $1 trillion by 2015. This increased production provides increased opportunities for unintentional exposures and unanticipated consequences of intentional use. Despite the proliferation of these materials, little is known about their interaction with biological systems, a condition that has generated significant concern. The same unique chemical and physical properties that make nanomaterials so potentially useful also make their interactions with biological systems difficult to anticipate and critically important to explore.

The NIEHS in partnership with the Trans-NIH Task Force, invites participation in a broad-based initiative that integrates research in material sciences, basic biology, and pathobiology with training. This initiative will employ state-of-the-art technologies to enable research to examine the fundamental physicochemical interactions of ENM with biological systems at the molecular, cellular, and organ level, as well as associated pathophysiologic processes. This research is critical for design of ENM with maximum human and environmental biocompatibility and safety. It will provide the biomedical research community with new knowledge of molecular, cellular, and organ system biology and identify clinically relevant properties of ENM. Moreover, this highly integrated research and training program would support U.S. goals for commercialization and innovation in nanotechnology through the safe development of ENM.

Background on ENM

The dimensions and quantum properties that emerge at the nanoscale enable novel applications. In addition to size, the surface area—to–mass ratio, shape, crystal structure, surface chemistry, and surface defects of ENM elicit electrical, optical, and magnetic properties, as well as biological behavior not observed in corresponding materials at the macroscale.

The nanoscale size of ENM enhances systemic transport, for example transport across the blood-brain barrier, across endothelial membranes into the vasculature, and through nasal sensory neurons to the olfactory bulb and the brain. And evidence continues to document nanoscale particulate translocation through intact stratum corneum, although these data are somewhat controversial. The large surface area–to–mass ratio of single ENM particles supports increased chemical reactivity per unit of material. However, the hydrophobicity of many ENM causes single particles to form aggregates and agglomerates, which may have a size-dependent decrease in propensity for systemic transport, altered chemical reactivity due to decreased surface area–to–mass ratio, and may or may not retain their quantum properties. Aggregates also may form or dissolve *in vivo*, thus complicating analysis of biological response and highlighting the effect of the microenvironment on ENM behavior. The nanoscale size and surface area–to–mass ratio of ENM challenge traditional concepts of dose and biological response. In a traditional dose–response relationship, the dose of a material is measured in units of mass and that mass measurement is related to the magnitude of the biological response. Several studies have explored the relationship of mass measurement of nanomaterials and the surface area of that mass to the biological response. The results suggest that, for certain ENM, surface area is a more accurate correlate of biological response than mass measurement, whereas other data suggest that neither surface area nor mass, but surface reactivity, is the critical parameter. The ENM characteristics and exposure conditions for which surface area or surface reactivity is the more accurate measure of dose have not yet been defined.

The specific aspects of design and synthesis of ENM that create unique physicochemical properties also will influence biological activity. Several studies suggested that ENM with highly derivatized surfaces permit cell growth and differentiation, while other materials perturb homeostasis and activate protective response pathways. For example, certain nanostructures, or fullerenes (unsubstituted C60), but not others (hydroxylated C60(OH)24), cause in vitro cell death. Also, the neuroprotective activity of one type of fullerene (tris-malonyl-C60) is attributed to its ability to scavenge free radicals and inhibit all three isoforms of nitric oxide synthase, albeit with different potencies. Other studies have shown that ENM cause oxidative stress, inflammation, mitochondrial perturbations, and membrane disruption. Also, carbon nanomaterials cause double strand DNA breaks in cells-free systems and, thus, introduce the possibility of point mutations, mitotic recombination, and chromosomal loss and translocation *in vivo*. Examples of these responses exist for all major classes of nanomaterials: fullerenes, metal and metal oxide nanoparticles, carbon-based nanoparticles and nanotubes, and macromolecules such as dendrimers.

Pathobiological changes have been observed in ENM–exposed rodent models, including development and exacerbation of vascular, pulmonary, and neurological disease. Several laboratories have demonstrated that carbon nanotubes accelerate atherosclerotic disease in hyperlipidemic ApoE knockout mice, and that carbon nanoparticles are thrombogenic. ENM show potential for use as neuroprotective agents in neuronal tissue engineering and as drug delivery systems that cross the blood–brain barrier, however, preliminary studies have shown that fullerenes induce potentially harmful lipid peroxidation in the brains of large mouth minnows. In murine models, ENM exposure has induced pathobiology

consistent with atherosclerosis and cardiac inflammation, fibrosis, granulomatosis, and emphysema.

Scope of the Initiative

This initiative outlines an integrated, interdisciplinary program that draws on the expertise and interests of the NIH institutes and centers, and addresses critical research needs for the safe development of ENM and nanoscale devices. The initiative has the following components:

- Materials Science Research — characterization of the physical and chemical properties of ENM in relevant biological systems;
- Basic Biology Research—determination of the relationship of nanoscale size and physicochemical properties to biological response at the cellular, molecular and systemic levels;
- Pathobiology Research—investigation of the relationship of nanoscale size and physicochemical properties to ENM-induced pathophysiologic endpoints and the development of disease;
- Informatics – a data-sharing framework to store and structure information on the potential environmental, health and safety risks of ENMs with data-mining, query, and search capabilities; and
- Training Program—education of scientists to work on cross-disciplinary and interdisciplinary nanotechnology research teams, and to develop research programs that integrate materials science, biology, and pathobiology research.

A partnership of NIH institutes, federal agencies, and private organizations is needed to fully embrace this initiative to pursue the very best science, avoid duplication of effort, leverage investment, and minimize the time from research to application. The structure of this initiative will be flexible in order to accommodate new projects, new partners, and research needs that emerge during the course of the research and training activities. The NIH recognizes the importance of nanomaterials safety research to the public, and will seek to incorporate a stakeholder advisory group into the research framework.

Materials Science Research

The rapid pace of nanotechnology development has created the need for targeted research to address questions that benefit the entire field and improve the quality of data and data reporting.

Dose Metrics. The large surface area–to–mass ratio of ENM, as well as highly reactive surface chemistry, suggest that traditional mass measurements may be insufficient or inappropriate to understand the relationship of dose to biological response. While mass remains an important measurement, evidence has been published for and against the inclusion of surface area, surface reactivity, particle number, and particle size distribution. More recent studies suggest that the surface electron energy status and the number of surface defects per particle are more accurate predictors of the magnitude of biological response. Still others suggest that crystal structure and shape will be critical components of a dose metric. The number of possible parameters and the lack of substantive research make delineation of the dose metric a complex question that can be addressed through targeted studies with clearly defined goals.

Routes of Exposure and Magnitude of Uptake. The behavior of nanomaterials in air and water differs from that of macroscale materials. For example, nanoparticles in air behave as a gas and may remain suspended indefinitely. In contrast, several laboratories have reported that nanoscale particles, unlike macroscale particles, penetrate intact stratum corneum and reach the epidermis and dermis, locations in which ENM may induce a cellular response or enter the blood stream or lymph. These differences in particle behavior at the nanoscale level will directly impact the internalized dose that is available to the body. Additional confounding factors, such as the effects of shape and electrical charge on uptake, have not yet been evaluated. Systematic analysis of size, shape, and electrical charge on ENM uptake for each of the exposure routes would inform these questions.

Minimal Information Reporting Standards. The complexity of dose metrics, coupled with the complexity and non-uniformity of design and execution of nanotechnology experiments, demonstrate the need to define more clearly how biological data on ENM are obtained. Minimal information reporting standards have been developed for microarray data, and are under development for proteomic data. Minimal information reporting standards ensure that data can be easily interpreted, compared, and verified, and should facilitate the entry of such data into multi-user databases and enable better data analysis. While not simple to achieve, minimal information standards should improve reporting in new fields with large amounts of rapidly accumulating data, and provide a basis for comparison of data sets and resolution of data conflicts.

Basic Biology Research

Although it is known that the human body is capable of a limited set of responses to exogenous and endogenous forms of stress, and that these responses can be evaluated through well-established biological assays, unique ENM properties suggest the possibility of novel biochemical, molecular, and cellular behavior in response to exposure. The Basic Biology Research component of this initiative will pursue critical questions that identify the molecular and cellular processes through which essential homeostatic mechanisms such as oxidative stress, inflammation, apoptosis, mitochondrial damage, and DNA repair are altered, and seek to link the novel size and size-dependent physicochemical properties of ENM with molecular and cellular responses.

Molecular and Cellular Studies. Cellular homeostasis is maintained by tightly controlled and integrated molecular networks. ENM–induced cell phenotypes provide indirect evidence for ENM interaction with fundamental cellular processes such as cell cycling, vesicular trafficking, transcription, respiration, and energy metabolism, and with cell-specific processes such as apoptosis, inflammation, and immunity. ENM could impair a functional pathway or,

through biocompatible design and engineering, facilitate repair of a dysfunctional pathway. Interaction of ENM with proteins, lipids, and nucleic acids in these critical pathways has not been investigated and represents a significant, unmet research need.

Membrane Dynamics. The barrier function of cell membranes is crucial for maintenance of cell structure and metabolism. The plasma membrane defines the intracellular space, and intracellular membranes create enclosed, functionally specialized compartments. These hydrophobic, lipid bilayers block transit of polar entities, however, cells have evolved multiple transport mechanisms to move ions and molecules into and out of cells and compartments, as well as transmembrane signaling pathways to communicate information across membranes. Disruption of membranes and membrane-supported events has profound consequences for cells and organ systems.

Many ENM are hydrophobic and able to partition easily into cell membranes, potentially disrupting the organization of the lipid bilayer, and its structural relationship to the membrane proteins, and consequently, the function of the membrane proteins. ENM may enter cells passively through endocytic transport or, if they fall within transport criteria, traverse channels and pores. Several laboratories report receptor-mediated uptake of ENM, carbon nanotube intercalation into plasma membranes, and cell-specific differences in ENM toxicity based on membrane behavior. For example, fullerenes cause fibroblast toxicity through lipid peroxidation of the plasma membrane and macrophage toxicity through lipid peroxidation of intracellular membranes and the plasma membrane. Differences in membrane composition and dynamics translate into differences in cell and organ system ENM uptake, intracellular sequestration, and systemic transport. While these pathways can be exploited for improved ENM drug delivery, they may
also adversely affect cellular structure and function.

Periodicity of the Biological Response to ENM. ENM present an opportunity to characterize a precisely engineered series of structurally and chemically related materials. Materials cientists report nanoperiodic relationships for dendrimers and quantum dots and hypothesize that nanoperiodicity is a feature of ENM that can be exploited for applications in industry and medicine. Size, shape, and chemical reactivity are considered critical components of nanoperiodicity, as are features that influence periodic patterns in physical properties, chemical stoichiometry, and steric effects, among others. This aim will investigate the hypothesis that physicochemical periodicity of ENM will result in biological periodicity, a concept that may be thought of as a stepped progression in a biological parameter as a function of a stepped change in a physical parameter. Early evidence for biological periodicity is suggested by the ENM dose–oxidative stress response, a correlative relationship that implies scalable and potentially controllable relationships between ENM and a biological activity.

Pathobiology Research

Research has documented that ENM can alter basic homeostatic pathways, such as inflammation, and oxidative stress pathways that may affect the development and exacerbation of disease. Vascular and pulmonary pathophysiology is linked, in part, to the efficiency of particle clearance, a process that in ENM is influenced by particle size and composition. Several laboratories have reported that single metal nanoparticles and small agglomerates evade macrophage engulfment, whereas quantum dots were observed in endocytic vesicles weeks to months after exposure. In rodent studies, inhaled nanoscale metal oxides caused significant increases in air-blood barrier permeability, macrophage accumulation, disruption of alveolar septa, and type II pneumocyte hyperplasia up to one year after a single aerosol exposure. ENM exposure has induced pathobiology consistent with atherosclerosis and cardiac inflammation. Additional pathways activated by ENM and associated with disease include cell cycle, apoptosis, immunity, and complement cascades. These data are derived from many classes of ENM, but no systematic study has yet identified the physicochemical properties of ENM that link these pathways to disease. Studies supported under this component of the initiative will extend the understanding of ENM disruption of homeostasis to ENM-induced pathophysiology.

Informatics

In order for the large amounts of data that will be collected in conjunction with this initiative to foster sound risk assessment and risk management decision making, the data must be standardized, stored, structured, and shared in an organized manner. To this end, a data-sharing framework for ENM's will be created. This framework will aggregate and store the data obtained from characterizing the physical, chemical, structural, mechanical, and biological properties of nanomaterials.

The informatics infrastructure will provide a structured repository for the data collected by the three research communities. It will also serve as a forum for communication between materials science, basic biology, and pathobiology researchers and facilitate modeling and evaluation of materials in new environments. Such a resource is expected to accelerate the transition from developmental research to health-related translational research; provide a forum for biologists and toxicologists to provide feedback to the developers of nanomaterials; and promote data standards, metrology standards, and validation standards for the development of nanoscale materials. The informatics component will thereby enable improved data integration; facilitate and incentivize data sharing; allow for efficient search and querying of data on engineered nanomaterials; provide the foundation for computerized decision support and modeling systems; and enable data-mining to discover new insights into structure-function relationships.

Training Program

In order to design and implement the kinds of cross-disciplinary and interdisciplinary research that will be necessary to fully understand how the novel attributes of ENM contribute to their biologic effects, a cadre of new investigators who are able to work in interdisciplinary ENM

research teams must be developed. These individuals will need to have training in several disciplines including exposure assessment, molecular and cellular biology, physical chemistry, materials science, engineering, and disease-based research, that, to date, have had little interaction. To develop meaningful collaborations, these researchers will need to have strong expertise in their chosen fields as well as knowledge in these other fields. Training opportunities will need to be developed at the predoctoral level where young investigators can be cross-trained in several disciplines, as well as at the postdoctoral level where such investigators can complement their previous training in one discipline with training in another. In addition, career development programs to allow new and more established faculty to expand their skills and, hence, their capacity to work in interdisciplinary teams would be appropriate. Many of these training opportunities could be developed within the context of established NIH training grants and fellowship programs. However, given the breadth of expertise envisioned, joint programs with other federal agencies or with private organizations or professional societies might be necessary.

Summary

Findings obtained through this initiative will establish standards for material sciences, determine biological thresholds, and address disease-based concerns for the emerging field of nanotechnology. This will be accomplished through scientific discovery followed by publication of standard setting reports in high quality, peer-reviewed journals, thereby creating a level of discourse that will facilitate debate of the controversial issues in this field. Data will be integrated into a data-sharing framework that will enable improved collaboration amongst materials scientists and biologists, promote rapid and targeted ENM development, and facilitate risk assessment. Fundamental research will inform the development of industrial, medical, and consumer products, and provide critical data for regulatory agencies.

Meeting Summary
NanoHealth Enterprise: Exploring Opportunities for Partnerships
9 October 2007
National Institutes of Health
Bethesda, MD

Sponsors: National Institute of Environmental Health Sciences (NIEHS)
National Institute of Biomedical Imaging and Bioengineering (NIBIB)

Attachments: Agenda
Attendees List
Presentations

Purpose: This meeting was the first step in an NIH effort to engage individuals from government, industry, academia, and public health advocacy groups to consider research partnerships to investigate the fundamental interactions of engineered nanomaterials (ENM) with biological systems. These partnerships would be developed through a NanoHealth Enterprise Initiative, and the results would support safe commercialization of nano-enabled products for medicine, industry, and consumer goods.

Format: Presentations identified broad research themes in nanomaterials health and safety research, informatics requirements for organizing and mining data, and models of partnership. Each presentation was followed by a lengthy discussion that focused on shared scientific questions, the purpose of partnerships, and models of partnership. The discussion has been synthesized into research needs and challenges and models for partnerships.

Working Timeline:
October 18, 2007—NIH organizational phone call
Between November 26 and December 7, 2007—pre-working group meeting to plan working group meeting
Within January 15–30, 2008—First working group meeting

Discussion:
General Comments
- Industry representatives discussed the need for predictability in order for industries to be able to invest in nanomaterials research and product development.
- Building literature base is important when building the foundation to a new scientific endeavor.

Research Needs
- Potential topics of shared scientific interest and high impact include:

- basic physical characteristics of nanoparticles;
  - tool and methods development for exposure measurements and chemical characterization,
  - structure-activity relationships for predicting biological response, QSAR;

- Research on pre-competitive materials is important to industry partners
- A clear and realistic timeline is important
- Evaluation and milestones will be necessary at each step of the process so all partners are assured they are getting what they need
- Several participants requested help from government agencies to
  - narrow the focus of nanomaterials health and safety research questions
  - set priorities by using a risk assessment focus and considering immediacy of research impact

Research Challenges

- Identifying and prioritizing shared research questions
- Developing a research program/strategy for diverse industries with different needs, different questions
- Perceptions and biases
  - general public view that industry research provides biased answers
  - broad perception that government is too unwieldy and difficult to work with
  - need for active management of real or perceived conflicts of interest – NIH review process could help with this
- Ethical, legal and social implications of nano-enabled products must be considered

Partnerships: Models and Challenges

- Models:
  - FNIH Models
    - leveraged funding by industry and government on mutually agreed upon questions
    - parallel funding by government and industry on same/similar questions
  - HEI partnership model: carefully managed contracts allow public to trust results
- Considerations:
  - federal agencies may have a role as coordinator but also a lead in setting priorities based on public need
  - industry collects data and government provides analysis
  - government needs to continue to work to remove barriers to partnership with industry
  - startup companies need an opportunity to participate

- overarching partnership is possible with diverse small projects addressing different questions; offers networking, consensus building, management of conflicts of interest
- use of several partnership mechanisms may offer maximum flexibility

Meeting Outcomes

- Partnerships arise where questions overlap
- Suggestion to have eventual separate scientific and management working groups
- Strong agreement to establish a "pre-working group" to organize efforts toward partnership and establish agenda for the first working group meeting
- Call for volunteers and invitation to others not in attendance for pre-working group

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Below are the notes (in blue) taken at the NanoHealth Enterprise Meeting. Presentations will be listed on the NanoHealth Enterprise Website.

NanoHealth Enterprise Coordination Meeting
Sponsored by the National Institute of Environmental Health Sciences
National Institute of Biomedical Imaging and Bioengineering
Bethesda, Maryland • January 16-17, 2008

Day One

7:30 **Breakfast and Registration**

8:30 **Welcome and Introduction**

- *Sam Wilson, Acting Director, NIEHS*
  - Indicated the overview of the process (governance, projects, review of projects)
  - Goal of effort: collaboration, leverage expertise, bring together funding/new funding, accelerate projects, enhance technology development.

- *Belinda Seto, Deputy Director, NIBIB*
  - National institute of biomedical imaging and bioengineering. Apply engineering principles to technology development and also bring in informatics.

8:45 **Overview of the Meeting Program** – *William Heetderks*

- First meeting was on October 9, received volunteers (around 25 people attended)
- Nov 30 planning meeting was held to develop agenda for January meeting
- Overview of surveys from registrations 42 public health, 59 research, 10 regulatory, 6 pharm, 16 biotech, 9 manufacturing, 6 semiconductor, 24 other legal ed policy
- Interests from survey: characterization, safety in workplace, environmental impact, biological app, toxicology, development of new nanomaterial, standards, regulatory aspects (FDA, OSHA, EPA)
- What do you expect to get: $, collaborations, regulations, interactions with regulators, access to database, and access to laboratories doing research.

9:00 **Focusing the Science**

Review of the critical questions to understand nanobiointeractions - *Sally Tinkle*

- Will focus on biology of materials
- Applications: to design materials for a specific purpose or use
- Implications: goal to minimize adverse effect on human health and environment.
- What is the overlap between applications and implications. All have interest in the overlap in the interaction of engineered nanomaterials in biological systems.
- Bring together the applications/implications and develop structure activity and dose response question>>>>develop computational models for safe design.
- What do we mean with respect to structure activity
  - Material synthesis>environ exposure>contact>internal dose>biological response>clinical disease (what about susceptible populations.
- Projects:
  - Dose metrics
  - Uptake by route of exposure
  - Interaction with biological fluids
  - Informatics Resource (use information about the materials to help with material design)
    - How can we capture biomedical application data for implications research?
- Broader research questions
  - Interaction with biological molecules
  - Inflammation and immunity
  - Exacerbation of existing disease
- Shared research products
  - Relevant design principles, curated data sharing framework, network of research partners

- Need to consider strategic product desingn and development, look at these kinds of products
- Human health research needs (consistent with NNI)
  - Quantify and characterize
  - Relationship between exposure, uptake and body burden
  - Absorption and transport
  - Mechanisms of interaction
  -
- NIH has its own nanohealth initiative
- Currently an NIH nanoengineered research program. Across NIH there is a therapeutics, diagnostics program. Questions about kinetics and clearance of materials. Very precise design and can capture information in database. (not a formal program at this point)

Review of existing nanomaterials characterization tools/methods/protocols for investigating nanobiointeractions – *Marty Fritts*

- From nanomaterial characterization laboratory
- Will focus on tools/platforms/informatics
- Characterization of ENM
  - Problems with characterization: lack of methods, batch to batch consistency, scale up synthesis
  - What has worked
    - Nanotechnology Characterizaiton Laboratory (NCL); NCI, FDA, NIST)
    - Available to all investigators from academia, industry, and government
    - Goals : standardized methods, SAR,
  - Current capabilities
    - Requires new tools and metrics
      - Size, distribution, topology, shape, net charge, zeta, targeting agents, imaging agents, therapeutics, composition, purity (residueal solvents, free components), stability (thermal, ph, phot)
      - Requires in vitro work as well: sterility, cell uptake/distribution, blood contact properties, toxicity (NCL Methods)
  - NIST has new reference materials (gold nanoparticles 10, 30, 60 nm particles and amine terminated and hydroxyl terminated G6 dendrimers)
  - Will be evaluating bioassays using standardized protocols.
  - Interference of ENM in traditional assays
    - False negatives due to sorption, surfactants, luminescence quenching
  - Gaps in metrology: separation sciences
    - Multistep synthesis (if you attach a therapeutic, targeting agent, and imaging agent) you will wind up with a mix of particles that have a variety of particles having a variety of functional groups added to a particle
    - Need to have a tool for evaluating batch consistency
    - Evaluate polydispersity using electron microscopy (3D TEM Tomography) Reference: Sougrat R et al. PLoS Pathogens Vol. 3, No. 5. Electron tomography of the contact between T cells …. http://pathogens.plosjournals.org/perlserv/?request=get-document&doi=10.1371%2Fjournal.ppat.0030063&ct=1
  - SEM-EDX used to evaluate TiO2 in process of material development.
  - Immune system response associated with the charge of a particle. Massive response with a positive charged particles.
  - Based on these data can start developing a model based on biocompatiablility, charge, solubility.
- Modeling and simulation
  - Needs in model
    - Detailed design,
    - Functionaliztion
    - Design and control in synthesis process

        - Interaction with imaging
        - Biocompatability
        - PBPK
    - Antigenicity of fullerences Columbia university (proc national academies of science)
- Nanoinformatics
    - Critical gaps
    - Needs open source, open development, open access, federatied. Local control of databases. Mechanism to link data (e.g., concept code), to link a FDA code with a agent code.
    - Current capabilities
- Bottom line
    - Need achievable goals for a collaboration and identify critical gaps

10:00 **Break**

10:15 **Perspectives on a Public-Private Partnership (PPP): *What's the view from your sector?***

– *Annette Kolodzie, Skip Rung*

• What could a NanoHealth PPP do that couldn't be accomplished some other way?
• What would compel our organization to participate in the PPP (What benefit must you get)?
• What expertise or resources would our organization bring to the PPP in order to get the expected benefit?
• What obstacles do I see that would hinder the PPP from being productive?

Sector Presentors:

Large/Medium Industries

• *Keith McIver*, Boeing
- Similar issues as described by Marty Fritz. Boeing is also in several partnerships with other companies/universities.
- Quality assurance and consistency of materials.
- Heavy investment in private partnerships in China and Australia
- Expertise bringing to table>>>level of standards and quality control. Ex. Aerospace, scrap metal from Boeing is used for sporting goods.
- Obstacles: funding, collaboration, united front. Lot of investment in government. NNI will help put standard framework together. NNI centers are somewhat duplicative.

• *Michele Ostraat*, RTI/NOSH Consortium
- Communication of results, rapid and broad
- Get critical buy in from regulators; what do results mean from regulators
- Get broad buy in from stakeholders
- RTI could bring technical and organizational expertise
- Independent analysis of results; financial resources provided.
- Identifying program organization.
- Formal agreements not accepted by broad membership; potential exclusion of members, no buy in by regulatory members
- Avoid bureaucracy, red tape.

• *Annette Kolodzie*, FEI • Pharma representative (tentative)
- Makes electron microscopes
- Comittment of fed agencies with these responsibilities: provide direciton for approach to evaluate EHS issues for nanomaterials.
- Evaluate investments to move forward; standards
- Communicate early and directly; can make ROI calculations based on certainty
- Need clear projects with clear milestones.
- Contribute expertise and training for microscopes, use of tools, electron microscopy and equipment.
- Don't take too long.
- Misalignment of objectives

• *Kevin Carl*, Novartis

- Have experience with NIH biomarker consortium
- Expertise sharing
- Regulatory standards development
- Cross validate methods
- Ineffectiveness in adopting information/approaches
- PSC (protective safety consortium), set new standards for predicting renal toxicity.
- Have not had many good new drug leads; this may help?
- Technical development expertise

Small/Startup Industries

• *Sean Murdock*, Nano Business Alliance, myriad of businesses
- Leverage resources and expertise
- Important to understand wide variety of materials
- Doing this to accelerate technology development and inspire public trust and confidence; help insure workplace safety
- Channel participation of small businesses, maybe contribute materials and expertise.
- Obstacles; ROI, funding resources.

Charles Grause, Luna Innovations
- Make nanomaterials and final product
- Small volumes
- Eliminate uncertainty and get to consensus
- Imaging and therapeutics materials
- Bring resources to bear.
- Do not have resources to collect this type of data; definite added benefit for commercialization of their products
- Create a collaborative environment tried to start up. Consortium addresses issues that make sense in their business sector.
- Provide business decision points, reduce time to market. Only a limited amount of time and money.
- Get data and get everyone on same page; key commercialization plan.
- Limited capability, but most collaborations
- Obstacles, need to discuss material characteristics

Academic Consortia

• *Steve* ,
- 15-20 companies that pool money and give out to universities for research. Only fund graduate students. Invested around $1B in research. Members are demanding, expect return on investment
- Life cycles of semiconductor companies, don't last long
- Disparate interests in a non-competitive environment nano/bio lab on a chip for medical technologies
- Expect ROI, leverage member funds to get research conducted that is more than can be accomplished alone.
- Contribute $, access to diverse industry, expertise in managing research
- Limitations: cannot act quickly, not having adequate focus to ensure adequate ROI. Needs to be focused, have a deliverable.

• *Vicki Colvin*, International Council on Nanotechnology (ICON) Absent

• *Kang Wang*, California Nanosystems Institute (CNSI)
- Need a good model for rules of engagement.
- PPP from research to industry>help industry to grow
- Need to understand each other, offer education and training
- Can help attract partners, offer interdisciplinary infrastructure (10 core facilities for this research)
- Help solicit state government participation > need industrial private sector residents at your site.
- Potential problems: IP issues; lack of interest and money.
- Term of research, time and duration

• *David Pui*, U. of Minnesota, particle technology laboratory
- Center consisting of 7 companies and $8 billion in products

- US is currently stock piling 100 million respirators for bird flu epidemic; Beneficial relationships working with university; relevance in education

Public Health Advocacy

• *Andrew Maynard*, Woodrow Wilson Center
- Get science right that will inform policy decisions. What will this PPP provide to further these goals
- Lack of funding may be greatest inhibitor, as well as lack of focus, lack of relevance to policy decisions, lack of independence/credibility, engaging everyone at the table.
- Key environmental groups are not in the room. (is this an issue?) Need buy in to process.
- Decisions by EPA, OSHA, FDA are required; what is gold standard: Health Effects Institute (created by auto industry originally). Insulated process from influence by industry and epa.

Federal Agencies

• Materials–*Eric Steel*, NIST
- Federal agencies are driven by mission. Mission to measurement, science and standards for technologies.
- Know critical need for NIST to be major player.
- Need matched mission. Need to get a technology road map to design the best solution to work on current and future issues.
- Need industry road map, regulatory environment based on reliable measures and standards. Need to understand partner competencies.
- Budgets are tight within federal agencies; circle wagons and do own stuff. Need to partner.
- Can bring measurement science, standards, propagation of reliable measurement methods to use and trust.
- Excellent suite of facilities and standards; already have a great deal of partnerships. Ex. Standard development.
- Obstacles: Intellectual property and propriety information; communication and implementation across cultures; industry profit and agency mission
- Conflicting priorities

• Research–*Nora Savage*, EPA
- Communication challenges can e a problem
- Can bring to table: lessons learned and what can be learned from global community and research needs
- Fertilize ground with different perspectives and increase yield.
- Have handle on critical research needs and right questions to ask at what time. Research needs document is broard, but which need to be answered now?

• Regulatory–*Rick Canady*, FDA
- Multiagency research needs, where do agency missions overlap and how do they connect.
- IP issues can be problems,
- PPP may bring 3rd party repository that may attract additional information.
- Analytical techniques and leveraging resources, exploration of generalizable properties for a wide variety of materials.
- Understanding of risk needs.
- Benefit of having regulatory program involved in discussions.
- Joint research and projects…apply to foods
- Obstacles; bad balance between data availability and protection

12:00 **Lunch**

1:00 **Ground Rules for Working with NIH** – *Barbara Mittleman*

1:10 **PPP Concepts and Strategies from the FNIH Perspective** – *Daniel Carucci*

1:25 **Breakout Dialogue #1: *Identifying participant and cross-sector requirements for building the NanoHealth Enterprise***

• Charge to the breakout groups – *Skip Rung*
- First ½ hour will be covering the issues associated with a partnership.
- Science questions

- Identify several projects that are critical for field
- Topic and deliverables

3:30 **Break and Report Editing**

4:00 **Group Reports and Discussion** – *Annette Kolodzie*

Group 1:

1. Develop a knowledge base/databased: cover existing publications (products and studies)
2. Isssue: financial sustainability of PPP

Group 2:

1. How to characterize NMs
    a. Find set of characteristics that are important to a sector
    b. How to do the characterization
2. Modeling may not be accurate
    a. Need to do predictive modeling to determine if this is achievable.
    b. If it is easier to do the measurements, then don't need the modeling.
    c. PPP should do something ground breaking
    d. No single group can do this?
    e. The problem with multi-dimensional materials cannot be done through a structure activity relationship.
    f. For example, if you have a quantum dot that changes functionalization in the body, a model will have a hard time with this.

Group 3: focused on the projects

1. Understanding or developing a drug development pathway, understanding where it will fail
    a. Translation from in vitro > in vivo and mouse to human
    b. Particulate versus chemical considerations
2. Are current tox methodologies applicable to nanomaterials
    a. Develop test methods for nanotox
    b. Verification of current methods and applicability
    c. Characteristics of nanomaterials that are critical
        i. How do we characterize
        ii. What materials to select to evaluate
        iii. What assays to use?
3. How do we develop a rapid screening test for toxicity
    a. First do tox studies
4. Maintenance of a database of properties
    a. Can be used as a predictive tool
    b. First need to characterize and identify variables in database
    c. Need standard for data.
    d. Concept of reporting language for characterization
    e. Standardized assays and test measurements
5. Ability to measure nanoparticle in body
    a. Surface state of material and how surface changes
    b. Metabolism of material
    c. Nondestructive testing

Group 4.

1. Standardized methodologies for exposures and impacts of nanomaterials
2. Methodology was for characterizing exposure and effects
3. Characterization methodology
4. Computational model; develop a computational model for smart design
    a. Use 28 materials selected that cover a wide range of materials (OECD has 14 classes)
    b. Populate with concensus materials
5. Universal aerosol sampler by 2010
6. Modeling of impact. Computational models
7. Real time risk assessment in air.

TOP THEME

1. Material characterization

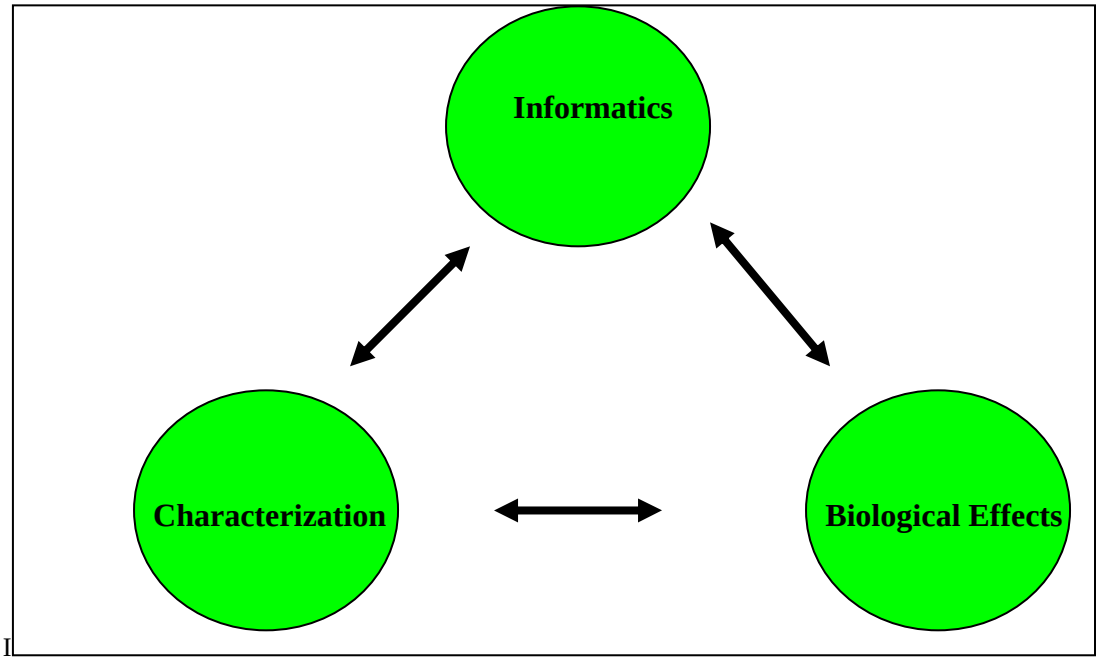
5:00 **Day One Wrap-up:** ***Identifying breakout topics for Day Two***
– Sally Tinkle, William Heetderks
5:15 **Ad Hoc Planning Members and Moderators Meet**

Day Two
8:30 **Recap of Day One** – *Sally Tinkle, William Heetderks*
8:45 **Breakout Dialogue #2: *Identifying the scientific projects we can do better together***
• Charge to the breakout groups – *Michele Ostraat, Kang Wang*

1. Where do we want to be in 5 years? What is a 5 year goal for this topic?
2. Where do we want to begin, low hanging fruit? Projects?
3. How would this research goal integrate the other two areas
4. What interlab methods/comparisons should the PPP do to support this project and begin to populate the database?
5. What are this area's contributions and needs regarding modeling? How would we accelerate the process of modeling in each of these areas?
6. What scientific disciplines would need to be at the table to accomplish this goal? Who are the top 10 people in this area?
7. What is your role in this PPP goal (data producer, user, funder, regulator, etc?

10:15 **Break and Report Editing**
10:45 **Group Reports and Discussion** – *Steve Hillenius*

3 main groups: informatics, characterization, biological responses



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Biological Effects Group

1. Standard reference materials and characterization tools
2. Characterization and informatics
3. Universal models that already exist.
4. Contributions to modeling?: Where would funding come from and when?
    a. Granularity, hypothesis, decision needs, validation and utility.
5. What disciplines should be involved?
    a. Toxicity
    b. Bio, chem., comptox, phsycial character, pathology
    c. Imaging with stats
    d. Decision analysts

Informatics Group

1. In 5 years, create a "NanoHub" of characterization for nanomaterials
    a. International network for models and data; a health version of NanoHub/NSF is a good example
    b. Includes open source models
    c. Wide array of services and tools
2. Near term, in next year focus on a set of physical and biological characterization of five candidate nanomaterials in several different species.
3. Stacey Harper will lead and help organize this meeting.

Characterization

1. Measurement and consistency is important; preparation of samples, measurement
    a. Consistency versus accuracy
    b. Components of characterization
2. Define what we can measure right now and its accuracy. 4 main goals:
    a. Understand minimum data requirements for characterization
    b. How to measure biologically relevant surfaces for airborne exposure
    c. Develop universal aerosol samples
    d. Characterize materials in the systems level (size, surface area) in a certain media without modification of that media.
3. Characterization requires input from other disciplines
4. Consistency is king
5. keep good data
6. Guidance to industry will make NNI funds more useful.

11:15 **Summary: *What do you need to take back to your decision makers to engage them in building the NanoHealth Enterprise?*** – *Barbara Mittleman*
11:30 **Wrap-up and Next Steps** – *Sally Tinkle, William Heetderks*
Follow up

1. Who else needs to be involved in this process?
2. What is value of information?
3. Look for an action plan in near future.

12:00 **Adjourn**