Informatics and standards for nanomedicine technology

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Outline

- Introduction to the caBIG® Nanotechnology Working Group
- Overview of nanotechnology informatics challenges
- Research projects
  - Ontology development
  - PubNano resource
  - Data exchange standards
  - Structure-property-activity modeling
National Cancer Institute caBIG®
Nanotechnology Working Group

► Government
  ■ National Institutes of Health
    ■ NCI, NHLBI, NIBIB, NCL
  ■ Center for Disease Control
  ■ Food and Drug Administration
  ■ Environmental Protection Agency
  ■ ...

► Academia
  ■ Washington University
  ■ Pacific Northwest National Lab
  ■ Oregon State
  ■ Stanford
  ■ MIT
  ■ Georgia Tech
  ■ UCLA
  ■ ...

► Industry
  ■ Intel
  ■ Pennsylvania NanoSysten
  ■ ...

► Standards organizations
  ■ ASTM E56
  ■ ISO TC229

► Alliances and organizations
  ■ International Alliance for NanoEHS Harmonization
  ■ Oregon Nanoscience and Microtechnologies Institute
  ■ National Nanotechnology Initiative
  ■ National Nanomanufacturing Network
  ■ NCI Nano Alliance
caBIG® Overview (http://cabig.nci.nih.gov/)

- Bench-to-bedside biomedical research infrastructure
- Integrates basic research to clinical research to patient care
- Broad deployment
  - Extensible framework
  - Significant use outside the cancer domain
- Poised for significant growth

- Track clinical trial registrations
- Facilitate automatic capture of clinical laboratory data
- Manage reports describing adverse events during clinical trials

- Use NBIA repository for medical images including CAT scans and MRIs
- Visualize images using DICOM-compliant tools
- Annotated Images with distributed tools

- Access library of well characterized and clinically annotated biospecimens
- Use tools to keep an inventory of a user’s own samples
- Track storage, distribution, and quality assurance of specimens

- Combine proteomics, gene expression, and other basic research data
- Submit and annotate microarray data
- Integrate microarray data from multiple manufacturers and permit analysis and visualization of data

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Images courtesy of Juli Klemm, National Cancer Institute

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Working Group Scope

Nano WG current areas of focus

▶ Nano-TAB development *(enabling)*
  - Nanotechnology data sharing standards
  - Working draft ready
  - Community engaged
  - Need to focus on applications and standards

▶ NPO support and expansion *(enabling)*
  - Standard vocabulary and ontology for nanomedicine
  - Foundation established
  - Community engaged
  - Need to focus on support for nano-TAB and other annotation projects

▶ Nano-QSAR *(applying)*
  - Structure-activity relationships for nanomaterial-biological interactions
  - Community engaged; participants identified
  - Many potential areas of focus
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  ■ Structure-property-activity modeling
What is the problem? **Unrealized potential due to combinatorial complexity**

- Nanomaterials are small and diverse
- The promise:
  - High density
  - Improved biodistribution
  - Multi-modal applications
- The problems:
  - Combinatorial diversity
  - Difficult characterization
- **An important challenge!**

What is the problem? **Diversity of data**

**Size distribution data**

**Tissue biodistribution**

**Anti-tumor activity**

**Drug loading data**

**Surface morphology data**

**Preparation**

**Chemical composition of nanoparticle formulation**

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**Zeta Potential**

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<tr>
<th>Nanoparticle formulations</th>
<th>Zeta potential (mV)</th>
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<td>Control nanoparticles</td>
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<tr>
<td>Tamoxifen-loaded nanoparticles</td>
<td>25.4 ± 1.4</td>
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* Zeta potentials of the nanoparticle suspension in deionized distilled water were measured using the Brookhaven's Zeta PALS instrument.
* Mean ± S.D (n = 8).
What is the problem? *Disconnected resources and users*
Who are the stakeholders?

Nanoinformatics stakeholders

- Standards
- Industry
- Users of nanomaterials
- Producers of nanomaterials
- Policy
- Regulatory
- NNI
- FDA
- EPA
- OSHA
- Materials science
- New materials
- Device engineering
- Sensors
- Academia
- Exposure
- Biomedical
- Diagnostics
- Environmental
- Occupational
- Defense
- Energy
- NIH
- NIBIB
- NCI
- caBIG Nano WG
- PEN
- Nano Registry
- NIEHS
- NIOSH
- CDC
- EPA
- OECD
- ASTM
- ISO
- TC229
- E56
What does the community need?

- The nanomedicine community has an immediate need for nanomaterial informatics:
  - Understand nanomaterial toxicity and other biological properties
  - Search for existing data on nanoparticle synthesis and properties
  - Systematically represent nanomaterial structure and composition
  - Exchange nanomaterial chemical, physical, and biological data
  - Design nanoparticles, and other materials with custom properties for specific biological applications
Our solution

- Information exchange and analysis through
  - Data exchange standards
  - Ontology
  - Information resources

- Methodology development and applications in nanomaterial prediction:
  - Biological activities
  - Chemical and physical characteristics
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NanoParticle Ontology (NPO)

- Capture knowledge underlying nanomaterial
  - Preparation
  - Chemical composition
  - Physiochemical characterization
  - Biological function/behavior
- Basic Formal Ontology structure
- Initial focus on cancer diagnosis and therapy
- Current growth to include a broader range of nanotechnology concepts
- Supported by the caBIG® Nano WG
- Available through Bioportal

http://purl.bioontology.org/ontology/NPO

http://www.nano-ontology.org/

Example view into the NPO
A more detailed view of nanoparticle composition using the NPO
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PubNano nanomedicine resource

Nano-friendly interface to relevant:
- Ontologies (browse and search)
- Resources (semantic search)
- Materials (structural search)
- Literature (links back to relevant terminologies)
- News

Driven by:
- NCBO Resource Index
- Knowledge Encapsulation Framework (KEF)
caOBR adds caBIG resources to the NCBO Resource Index

- caOBR: connecting caBIG with Bioportal
- Use the NPO and other ontologies for *semantic* search
- caOBR adds caBIG resources to NCBO Index
- caOBR also exposes NCBO Index to caBIG

KEF features: Semantic MediaWiki for annotation, search, and evidence marshalling
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PubNano: coming soon!

Integration of:
- PubMed
- caNanoLab
- MICAD
- GEO
- ...

Coming soon to http://pubnano.bioontology.org!
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Nano-TAB for Nanomaterial Data Sharing
Target audiences and applications

**Audiences**
- Biomedical researchers
- (Nano)-Materials scientists
- Toxicologists
- Regulatory scientists
- Industrial hygienists
- ...

**Applications**
- Synthesis
- Therapeutics, diagnostics, imaging
- Bionics and prosthetics
- Risk and exposure assessment
- Toxicity prediction and reduction
- Laboratory and occupational safety
Goal of nano-TAB

Develop a specification to facilitate the import/export of data on nanomaterials and their characterizations to/from nanotechnology resources

Sample Identifiers

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Assay Name

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Assay Files

- NTP (NIEHS)
- NCL (NCI, FDA, NIST)
- NBI (ONAMI)
- InterNano (NNN)
- NIL (NIOSH)
What is nano-TAB?

► A standard tab-delimited format for describing data related to
  ■ Investigations
  ■ Nanomaterials
  ■ Specimens
  ■ Assays

► Leverages and extends the Investigation/Study/Assay (ISA-TAB) format
  ■ Standard tab-delimited file format
  ■ Developed by the European Bioinformatics Institute (EBI) for representing a variety of assays and technology types
  ■ Example: MAGE-TAB

► Nano-TAB supports ontology-based curation
  ■ Nanomaterials and concepts from the NanoParticle Ontology (NPO) as well as other ontologies
Uses and benefits

- Address the data sharing challenges in nanomedicine
- Provide a standard means for identifying nanomaterials and characterizations
- Enable the submission and exchange of nanomaterial data to/from nanotechnology data resources (e.g., NBI, caNanoLab, etc.)
- Empower organizations to adopt standards for representing data in nanotechnology publications
- Provide researchers with guidelines for representing nanomaterials and characterizations to achieve cross-material comparison
nano-TAB structure

1. Describe the Investigation and Studies
   - i_xxx.txt
   
2. Identify Study Samples
   - s_xxx.txt
   - m_xxx.txt
   
3. Record Assay Conditions and Measurements
   - a_xxx.txt

Investigation File
Study File(s)
Material File(s)
Assay File(s)
Nano-TAB Investigation File

- Describes
  - Primary investigation
  - Associated studies, assays, and protocols
- Descriptive information about the study includes
  - Design descriptors and factors
  - Publications
  - Assays and protocols
  - Contacts
- Vertical-based spreadsheet format with columns representing multiple values
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<td>The objective of the Dendritic Nanotechnologies, Inc. - NCL collaboration is to characterize a PAMAM dendrimer with an associated gadolinium chelate MRI contrast agent. The nanomaterials submitted for testing at the NCL were [NCL21] G4 bis (hydroxyl) terminated PAMAM dendrimer, [NCL22] G4 pyrrolidine terminated PAMAM dendrimer, [NCL23] G4 CDOs terminated PAMAM dendrimer, [NCL24] G4 bis (hydroxyl) terminated PAMAM dendrimer-Magnevist/e complex, [NCL25] G4 bis (hydroxyl) terminated PAMAM dendrimer-Magnevist/e complex, and [NCL26] G4 pyrrolidine terminated PAMAM dendrimer-Magnevist/e complex. Commercially available Magnevist/e (NCL24) was used as a control. NCL studies addressed in this report can be divided into three main categories: physicochemical characterization; immunotoxicology; in vivo toxicity.</td>
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</table>

Pacific Northwest NATIONAL LABORATORY

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Dynamic light scattering (DLS) technique was used to measure the hydrodynamic size of the dendritic nanomaterial. The effects of sample concentration, buffer, and temperature on the hydrodynamic size also were measured. Purity was analyzed by HPLC and Capillary Electrophoresis. MALDI-TOF Mass spectrometry was used to obtain the molecular weight information and to determine the purity, existence of dimers, trimers, and trailing generations in the sample. Gadolinium quantitation, which is important to determine the relativity as a MRI contrast agent, was carried out by Inductively Coupled Plasma Optical Emission Spectroscopy (ICP-OES). Fractionation methods such as Size Exclusion Chromatography (SEC) and Asymmetric-flow Field Flow Fractionation (AFFF) were used to determine the molecular weight information as well as purity. Finally, a 3T clinical MRI machine was used to obtain relativity measurements on this sample to compare with free Magnevist/E. No significant relativity change was observed upon association of Magnevist/E with the dendrimer.

For NCL22, the size is slightly larger when dispersed in saline compared to PBS. In PBS, the size is independent of temperature. This is in contrast to NCL23, which is larger in PBS than in saline. NCL23 also shows temperature dependence, as its size decreases slightly with increased temperature in PBS. Finally, NCL20 is larger when dispersed in PBS compared to saline.
nano-TAB structure

1. Describe the Investigation and Studies

2. Identify Study Samples

3. Record Assay Conditions and Measurements

- Investigation File: i_xxx.txt
- Study File(s): s_xxx.txt
- Material File(s): m_xxx.txt
- Assay File(s): a_xxx.txt

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nano-TAB Study File

- Study files provide mappings between the samples, materials, and processing events associated with a study.
- Samples can be
  - Biological materials
  - Nanomaterials
  - Small molecules
- For physical-chemical characterizations of nanomaterials, the sample is the nanomaterial.
- For in vitro and in vivo characterizations, the sample is the biological specimen (cell line, animal, etc.)
nano-TAB Material File

- Primary file for describing
  - Nanomaterial composition and formulation
  - Physical properties
  - Structure

- Allows for
  - Comparison of nanomaterials across nanotechnology resources
  - Association with optional files; e.g., a Structure file for representing the 3D structure of the nanomaterial

- Vertical-based spreadsheet with the following sections:
  - MATERIAL SAMPLE
  - MATERIAL COMPONENT
  - MATERIAL LINKAGE
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<td>Material Component File Version</td>
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### Material Linkage

#### Material Linkage Identifier

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<td>Material Linkage Type</td>
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<td>Material Linkage Type Term Source REF</td>
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#### Material Linkage Characteristics

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<td>Material Linkage Characteristic Statistic Term Source REF</td>
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<td>Material Linkage Characteristic Unit Term Source REF</td>
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nano-TAB structure

1. Describe the Investigation and Studies
   - i_xxx.txt
   - Investigation File

2. Identify Study Samples
   - s_xxx.txt
   - m_xxx.txt
   - Study File(s)
   - Material File(s)

3. Record Assay Conditions and Measurements
   - a_xxx.txt
   - Assay File(s)
nano-TAB Assay File

- Describes the protocol parameters and factors, including:
  - Temperature
  - Media/solvent
  - Concentration
- Provides references or links to assay results, including:
  - Measurements
  - Instrumentation
  - Derived data files
- Templates available for the “top Nano WG assays”
  - Size by DLS (Physico-Chemical)
  - Zeta Potential (Physico-Chemical)
  - Hemolysis (In Vitro)
  - Hepatocarcinoma Cytoxicity (MTT and LDH) (In Vitro)
  - Caspase 3 Apoptosis (In Vitro)
  - Toxicity (ADME, Single/Repeat Dose) (In Vivo)
  - *Your assay here!*
nano-TAB Assay File

- Horizontal-based spreadsheet format with the following sections:
  - SAMPLE NAMES
  - PARAMETERS
  - FACTORS
  - ASSAY MEASUREMENTS
  - ASSAY FILES
<table>
<thead>
<tr>
<th>Material Sample Name</th>
<th>Protocol REF</th>
<th>Parameter Value [pH of solution]</th>
<th>Parameter Value [NaCl concentration]</th>
<th>Performer</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCL-20-F1</td>
<td>Hydrodynamic Size/Size Distribution via Dynamic Light</td>
<td>7.4</td>
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<td>Anil Patri</td>
<td>2010:05:12</td>
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<td>NCL-22-F1</td>
<td>Hydrodynamic Size/Size Distribution via Dynamic Light</td>
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<td>2010:05:12</td>
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<td>Hydrodynamic Size/Size Distribution via Dynamic Light</td>
<td>7.4</td>
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<td>Anil Patri</td>
<td>2010:05:12</td>
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<td>NCL-23-F1</td>
<td>Hydrodynamic Size/Size Distribution via Dynamic Light</td>
<td>7.4</td>
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<td>Anil Patri</td>
<td>2010:05:12</td>
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<td>Hydrodynamic Size/Size Distribution via Dynamic Light</td>
<td>7.4</td>
<td></td>
<td>Anil Patri</td>
<td>2010:05:12</td>
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<thead>
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<tbody>
<tr>
<td>Size by DLS</td>
<td>25 celsius</td>
<td>UO</td>
<td>saline</td>
<td>5.2</td>
<td>z-average</td>
<td>nm</td>
<td>UO</td>
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<td>Size by DLS</td>
<td>25 celsius</td>
<td>UO</td>
<td>PBS</td>
<td>8.6</td>
<td>z-average</td>
<td>nm</td>
<td>UO</td>
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<tr>
<td>Size by DLS</td>
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<td>UO</td>
<td>saline</td>
<td>8.5</td>
<td>z-average</td>
<td>nm</td>
<td>UO</td>
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<td>Size by DLS</td>
<td>25 celsius</td>
<td>UO</td>
<td>PBS</td>
<td>6.6</td>
<td>z-average</td>
<td>nm</td>
<td>UO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Size by DLS</td>
<td>37 celsius</td>
<td>UO</td>
<td>PBS</td>
<td>7.9</td>
<td>z-average</td>
<td>nm</td>
<td>UO</td>
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<td>25 celsius</td>
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<td>saline</td>
<td>7.4</td>
<td>z-average</td>
<td>nm</td>
<td>UO</td>
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<td>25 celsius</td>
<td>UO</td>
<td>PBS</td>
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<td>z-average</td>
<td>nm</td>
<td>UO</td>
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<tr>
<td>Size by DLS</td>
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<td>UO</td>
<td>PBS</td>
<td>9.8</td>
<td>z-average</td>
<td>nm</td>
<td>UO</td>
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</table>
nano-TAB structure

1. Describe the Investigation and Studies
   - i Xxx.txt
   - Investigation File

2. Identify Study Samples
   - s Xxx.txt
   - Study File(s)
   - m Xxx.txt
   - Material File(s)

3. Record Assay Conditions and Measurements
   - a Xxx.txt
   - Assay File(s)
Getting Started

1. Contact us for help! nano-tab-l@list.nih.gov
2. Use nano-TAB template to create nano-TAB files: http://goo.gl/T7Mwi
3. Leverage template glossary for definitions: http://goo.gl/YkRZM
4. View example files: http://goo.gl/yKFew
5. Navigate the BioPortal ontology for terms: http://goo.gl/SVmNZ
6. Complete nano-TAB files and send to the nano-TAB Listserv: nano-tab-l@list.nih.gov

caBIG® Nano WG nano-TAB Site:
http://goo.gl/yKFew
# nanoTAB Template Glossary

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>2) MATERIAL</td>
<td>Section heading for the Material section. The Material section allows for the description of the nanomaterial formulation and any materials (including material parts) associated with the nanomaterial formulation. A formulation is the nanomaterial and any other components or medium. A formulation can also be any non-biological material sample (e.g., small molecule) used in experimentation.</td>
<td>NCO-28</td>
</tr>
<tr>
<td>3) Material Identifier</td>
<td>Unique internal identifier for the material</td>
<td>g45_cocoa_dendrimer_magnesivst_complex</td>
</tr>
<tr>
<td>4) Material Name</td>
<td>Unique name given to a material used to identify or reference the material across the nano-TAB files</td>
<td>g45_cocoa_dendrimer-magnesivst&lt;complex&gt;</td>
</tr>
<tr>
<td>5) Material Description</td>
<td>Text description of the material</td>
<td>G4 C ODDA terminated PANAM dendrimer-Magnesivst&lt;complex&gt;</td>
</tr>
<tr>
<td>6) Material Synthesis</td>
<td>Text description of how the material was made</td>
<td></td>
</tr>
<tr>
<td>7) Material Design Rationale</td>
<td>Property, process or phenomenon taken into consideration when formulating a material in order to achieve the intended use of the material. The value can be a textual description or terms that may be obtained from an ontology or controlled vocabulary.</td>
<td></td>
</tr>
<tr>
<td>8) Material Design Rationale Term Accession Number</td>
<td>Identification number of a term selected from an ontology or a controlled vocabulary, and entered as a value for the underlying Design Rationales.</td>
<td></td>
</tr>
<tr>
<td>9) Material Design Rationale Term Source REF</td>
<td>Name of the ontology or controlled vocabulary from which a term is selected and entered as a value for the underlying Design Rationales.</td>
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</tr>
<tr>
<td>10) Material Type</td>
<td>Names that describe the type of material</td>
<td>nanoparticle sample</td>
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<td>11) Material Type Term Accession Number</td>
<td>Identification number used within an ontology or a controlled vocabulary</td>
<td>NPO_1404</td>
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<tr>
<td>12) Material Type Term Source</td>
<td>Name of the ontology or the controlled vocabulary from which the term was selected, entered as a value for the underlying Design Rationales.</td>
<td>NPO_765</td>
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</tbody>
</table>
nano-TAB future

- ASTM ballot
- User guide
  - Basic descriptions of elements, glossary
  - Organized collection of examples
  - Tutorials
- Easier NPO annotation and integration
  - List of most relevant terms
  - List of missing terms
- Real world applications
  - “Client” engagement
  - Friendly user support

http://cananolab.nci.nih.gov/caNanoLab/welcome.do
http://nbi.oregonstate.edu/knowledgebase
nano-TAB is a community-driven effort
Additional nano-TAB reading and project team

- nano-TAB Project Site: http://goo.gl/yKFew
- ASTM nano-TAB Work Item WK28974: http://goo.gl/OjSOX
- ISA-TAB: http://isatab.sourceforge.net
- caBIG ICR Nano WG Data Standards Document: http://goo.gl/sDEvp
- NanoParticle Ontology (NPO): http://www.nano-ontology.org

Nano-TAB project team

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Elaine Freund, 3rd Millennium
Marty Fritts, NCL
Sharon Gaheen, SAIC
Liz Hahn-Dantona, Lockheed Martin
Stacey Harper, Oregon State University
Mark Hoover, NIOSH
Fred Klaessig, Pennsylvania Bio Nano Systems
Juli Klemm, NCI CBIIT
David Paik, Stanford University
Sue Pan, SAIC
Grace Stafford, The Jackson Laboratory
Todd Stokes, Georgia Tech
Dennis Thomas, PNNL
Summary

Introduction to the caBIG® Nanotechnology Working Group

Overview of nanotechnology informatics challenges

Research projects

- Ontology development
- PubNano resource
- Data exchange standards
- Structure-property-activity modeling

Collaborators

caBIG® ICR Workspace, NCBO staff, ASTM, Raul Cachau, Gilbert Fragoso, Elaine Freund, Marty Fritts, Sam Gambhir, Sharon Gaheen, Liz Hahn-Dantona, Stacey Harper, Mark Hoover, Fred Klaessig, Juli Klemm, Michal Lijowski, David Paik, Sue Pan, Rohit Pappu, Persistent Systems Ltd, Daniel Rubin, Stan Shaw, Dennis Thomas, Eddie Xu, Kilian Weinberger, Trish Whetzel, …and many more!

Funding

caBIG® ICR Workspace and the NIH NCI caBIG® Working Group, Pacific Northwest National Laboratory HHS sector LDRD funds, as well as NIH grants U54 HG004028 and U01 NS073457