Nanotechnology Characterization Laboratory

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
National Institutes of Health
National Cancer Institute

U.S. Food and Drug Administration

U.S. DEPARTMENT
OF COMMERCE
National Institute of
Standards and Technology

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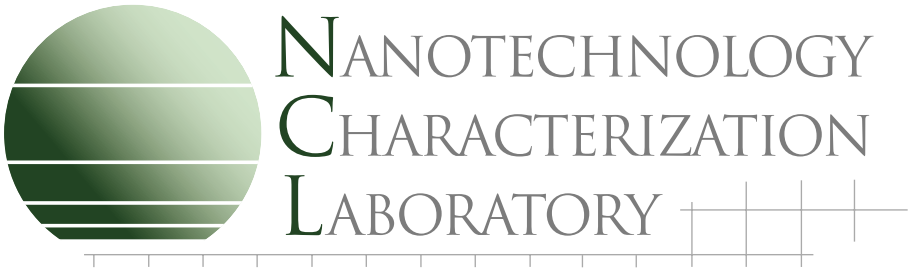
The Nanotechnology Characterization Laboratory is a collaborating partnership of the National Cancer Institute and the U.S. Food and Drug Administration of the U.S. Department of Health and Human Services, and the National Institute of Standards and Technology, U.S. Department of Commerce.



January 2005

Quick Guide for Prospective Applicants

The Nanotechnology Characterization Laboratory (NCL) enables researchers to transition their nanotechnology concepts to clinical applications by characterizing the materials' properties as they relate to biological systems. Applicants can apply to have their materials evaluated by NCL at no cost by submitting formal application materials and agreement to policies and terms specified.

How do I submit an application and what information is needed?

Prospective applicants should complete Annexes 1, 2, and 3 (Inside Back Cover) OR use the online application at **http://ncl.cancer.gov/working_application-process.asp#annexes**.

What criteria are needed for nanomaterials to qualify for analyses?

Entrance criteria for candidate nanomaterials are found on page 24.

What are the receipt dates for applications to submit nanomaterials to NCL?

First business day of March, June, September, and December.

What analytical tests will be done on the nanomaterials and what will be done with the data?

The types of analyses that will be performed on the nanomaterials are described on page 11. The goal of the NCL is to develop publicly available analytical data. The policies regarding data and information release are provided in Annex 3.

Where do I submit application materials and how can they be submitted?

Application materials should be submitted by mail or electronically (see Inside Front Cover for address). No faxes please.

INTRODUCTION

Achieving the National Cancer Institute's (NCI) Challenge Goal of eliminating death and suffering from cancer will require an unprecedented collaborative effort that leverages all available resources from government, industry, and academia. In support of this, the NCI is engaged in efforts to harness the power of nanotechnology to change radically the way we detect, diagnose, treat, and prevent cancer.

Nanoscale particles and devices, with size between 1 and 100 nanometers in at least one dimension, are similar in size to biomolecules and can easily enter most mammalian cells. Our ability to manipulate the physical, chemical, and biological properties of these particles affords researchers the ability to engineer and use nanoparticles for drug delivery, as image contrast agents, and for diagnostic purposes. NCI is establishing the Nanotechnology Characterization Laboratory (NCL) at its NCI-Frederick facility to provide critical infrastructure support to this rapidly developing field. The intent of the NCL is to accelerate the transition of basic nano-biotechnology research into clinical applications. The NCL will prioritize its resources to meet the following objectives within the next 5 years:

- Establish and standardize an analytical cascade for nanomaterial characterization.
- Facilitate clinical development and regulatory review of nanomaterials for cancer clinical trials.
- Identify and characterize critical parameters related to nanomaterials' absorption, distribution, metabolism, excretion, and acute toxicity (ADME/Tox) in animal models and cell lines.
- Examine the biological characteristics of multicomponent nanoscale platforms, including therapeutic, molecular and clinical diagnostic, and detection aspects.
- Engage and facilitate academic and industrial-based knowledge sharing of nanomaterial performance data and behavior resulting from pre-clinical testing (i.e., physical characterization, in vitro testing, and in vivo pharmaco- and toxicokinetics).
- Interface with national nanotechnology planning and coordination efforts, such as the National Nanotechnology Initiative, in cancer research, nanoscience and nanotechnology research, and health, safety, and the environment.

MISSION STATEMENT

The Nanotechnology Characterization Laboratory (NCL) will perform and standardize the pre-clinical characterization of nanomaterials intended for cancer therapeutics and diagnostics developed by researchers from academia, government, and industry. The NCL will serve as a national resource and knowledge base for cancer researchers, and facilitate the development and translation of nanoscale particles and devices for clinical applications.

Figure 1. Interface of Nanotechnology Characterization Laboratory activities with clinical nanotechnology platform developmental timeline.

ROLE OF THE NANOTECHNOLOGY CHARACTERIZATION LABORATORY IN THE NATIONAL CANCER INSTITUTE CANCER NANOTECHNOLOGY PLAN

To help meet the goal to eliminate death and suffering due to cancer, the National Cancer Institute (NCI) is engaged in a concerted effort to harness the power of nanotechnology to radically change the way we diagnose, treat, and prevent cancer. Using inputs from clinicians, cancer researchers, and technologists, the NCI has developed the Cancer Nanotechnology Plan (CNPlan) to meet these goals. The CNPlan (http://nano.cancer.gov) lays out a pathway and a set of mechanisms to facilitate nanotechnology becoming a fundamental driver of advances in cancer research.

During its development and due diligence of the CNPlan, NCI noted a widespread interest among cancer researchers in overcoming significant obstacles in order to transition nanotechnology to clinical application. These obstacles centered on three common themes:

- Lack of available reference data to compare results from various laboratories.
- Need for "first principles" of understanding about nanomaterials' interactions with biological systems.
- Undefined clinical development pathways for nanomaterials intended for cancer therapeutics and diagnostics.

To address and overcome these barriers, the NCI established the Nanotechnology Characterization Laboratory (NCL) at its NCI-Frederick facility. The charter of the NCL is to perform the pre-clinical characterization of nanomaterials and to facilitate the development of nanomaterials intended for clinical use. Focused development and pre-clinical testing of new technologies by the NCL characterization will facilitate entry of these products into clinical trials, and this will directly affect the number of new diagnostic and treatment strategies that reach the market, i.e., new drug approval.

NCL resources and activities will be prioritized to influence, inform, and accelerate the research and pre-clinical test phases for drug and device development, as shown in the timeline diagram of Figure 1. The NCL focus on the translational phase offers a supportive method for introducing and evaluating new mechanisms for accelerating test phases, improving and defining methods, and introducing novel nanotechnology strategies into clinical trials.

Courtesy HDR Architecture Inc./Steve Hall © Hedrich Blessing

NANOTECHNOLOGY CHARACTERIZATION LABORATORY PARTNERSHIPS

The activities within the NCL represent a formal scientific interaction of three Federal agencies: National Cancer Institute and U.S. Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services, and National Institute of Standards and Technology (NIST) of the U.S. Department of Commerce. Scientists from each agency bring critical knowledge, experience, and skills needed to establish information to facilitate clinical technology development.

National Institute of Standards and Technology

The interface of the physical and life sciences shows extreme promise for technological breakthroughs. With a 100-year history in quantitative physical measurements, NIST (http://www.nist.gov) engages in partnerships with industry, academia, and other government agencies to advance biosciences research, enable new health care technologies, and improve the quality and cost-effectiveness of health care delivery systems and processes. World-class research facilities, coupled with key competencies in the physical sciences, engineering, information technology, and, especially, nanotechnology, make NIST a unique and valuable resource to the bioscience community.

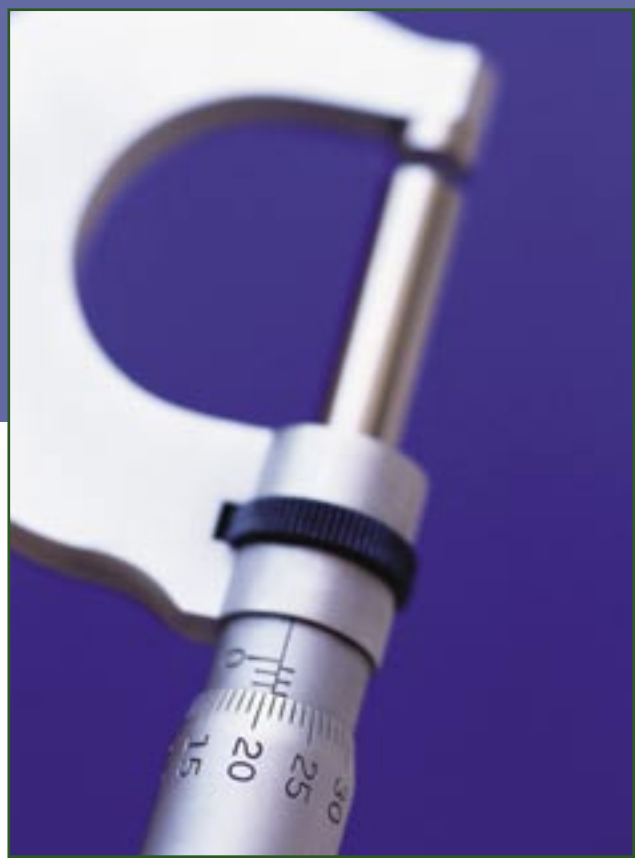
As an agency of the Technology Administration in the U.S. Department of Commerce, *NIST is charged with developing and promoting measurement, standards, and technology to enhance productivity, facilitate trade, and improve the quality of life*. The mission is carried out intramurally through scientific research in seven major laboratories, as well as extramurally, with three programs in close collaboration with U.S. industry: Advanced Technology Program, Manufacturing Extension Partnership, and Baldrige National Quality Program.

NIST intramural scientists and engineers number over 1,000, including two recent Nobel Prize winners. The Advanced Measurement Laboratory, a 500,000 square foot, $280 million research facility with a modern nanofabrication cleanroom, is just one of NIST's unique research resources available to partners.

Under the auspices of the NCL, NIST will work closely with NCI and FDA to develop quantitative, reproducible measurement methods and protocols for nanoparticle characterization. NIST will bring the physical characterization to the partnerships. NIST will actively engage in program planning and execution for the NCL and all associated workshops and meetings. Finally, NIST scientists will vigorously collaborate with NCI and FDA researchers to determine the best measurement tools, protocols, and analysis algorithms for physically characterizing nanoparticles.

U.S. Food and Drug Administration

FDA (http://www.fda.gov) has developed a strong and standardized model for evaluating diagnostics, has a new integrated regulatory program for regulation of diagnostic devices (Office of In Vitro Diagnostic Device Evaluation and Safety), and has begun to explore methods for evaluating multiplex technologies and for better incorporating new diagnostics into drug development when appropriate. While the agency has limited experience with nanotechnology, it has great interest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in developing mechanisms for facilitated review and ensuring rapid but science-based decision-making in regulation of this new technology. Examples of FDA's ongoing projects with NCI include:

- FDA/NCI clinical proteomics program – collaboration on nanoparticle harvesting agents for biomarker discovery
- FDA/NCI clinical proteomics program – development of new nanomaterials for protein microarray development
- FDA/NCI clinical proteomics program – nanotoxicology studies using phosphoproteomic signature analysis/signal pathway protein microarrays
- National Center for Toxicological Research (NCTR) evaluation of exposure to nanotechnology using gene expression microarrays

National Cancer Institute at Frederick

National Cancer Institute at Frederick (NCI-Frederick) (http://www.ncifcrf.gov) is part of the National Institutes of Health (NIH) and one of two NCI campuses. The NCI's clinical researchers, as well as the NIH Campus Center, are located on the NIH campus in Bethesda, Maryland. The NCI's Frederick campus is located within Fort Detrick, in Frederick, Maryland.

NCI-Frederick focuses on direct research aimed at identifying the causes of cancer, AIDS, and related diseases. More than 100 scientists here are investigating the genetic, molecular, environmental, and behavioral factors that contribute to human cancers as well as identifying new targets for cancer diagnosis, treatment, and prevention. NCI-Frederick also provides core scientific expertise and advanced technology development to NCI, National Institute of Allergy and Infectious Diseases, and other components of NIH via the Research Technology Program and other programs directed by SAIC-Frederick, Inc., a subsidiary of Science Applications International Corporation (SAIC).

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NANOTECHNOLOGY CHARACTERIZATION LABORATORY OBJECTIVES

1. Establish and Standardize an Analytical Cascade for Nanomaterial Characterization

Nanomaterials characterized by the NCL are intended for in vivo diagnostic and therapeutic purposes. To this end, the NCL will develop and perform a standardized analytical cascade that tests the pre-clinical toxicology, pharmacology, and efficacy of nanoparticles and devices. Nanomaterials received from academia, government, and industry will be subjected to this assay cascade that characterizes nanoparticles' physical attributes, their in vitro biological properties, and their in vivo compatibility. The time required to characterize a nanoparticle from receipt through the in vivo phase is anticipated to be 1 year, ultimately enabling a sponsor's filing of an Investigational New Drug (IND) or Investigational Device Exemption (IDE) application with the FDA. This sequence is shown in Figure 2.

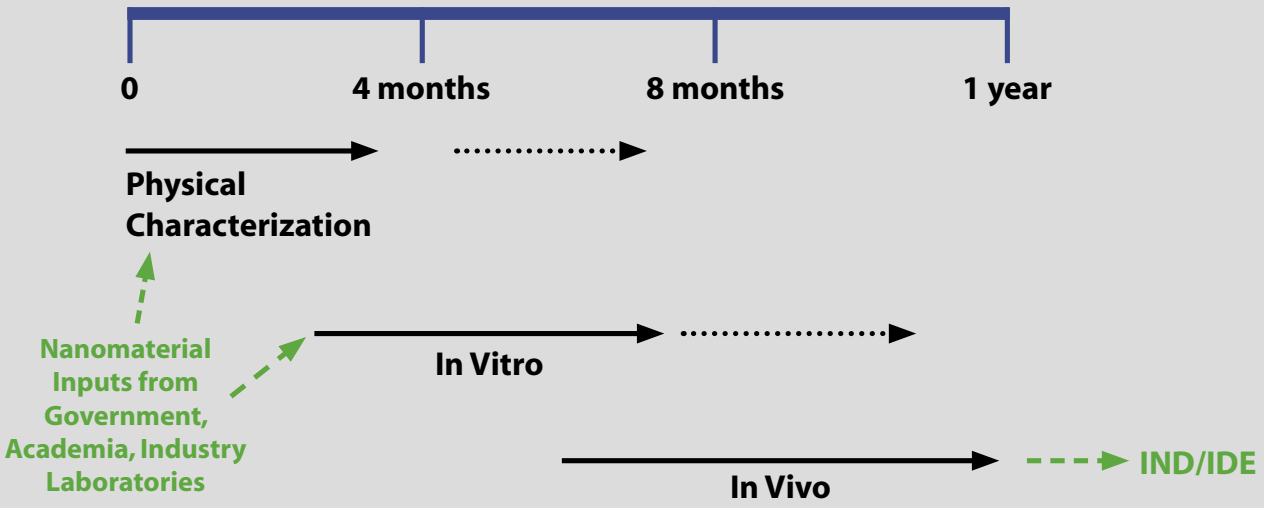

Figure 2. Estimated characterization timeline.

Physical Characterization

Current research on therapeutic and diagnostic applications for nanomaterial is helping to identify critical parameters for the material's compatibility with biological systems. Extant literature implicates physical attributes such as size, hydrophilicity, and surface chemistry as key factors contributing to a nanomaterial's in vivo fate. The first phase of the analytical cascade will therefore focus on characterizing the material's physical properties. The goal of this phase is to determine the particle's size, size distribution, molecular weight, density, surface area, porosity, hydrophilicity, surface charge density, purity, sterility, surface chemistry, and stability. The batch-to-batch reproducibility of material as provided by the sponsor/vendor will also be addressed during this stage. NCL will rely heavily on the expertise and resources of NIST for the physical characterization phase.

In Vitro Characterization

Prior to filing an Investigational New Drug (IND) or Investigational Device Exemption (IDE) application with the FDA, a new product must be adequately studied. For these products, toxicity or biocompatibility must first be characterized in animals and efficacy may be standardized in animal discovery models. The cost- and labor-intensiveness of these in vivo studies impel drug and device discovery efforts to utilize in vitro methodologies wherever technology permits. Refined in vitro protocols related to drug and device discovery allow researchers to make a first-order assessment of a material's in vivo pharmacokinetics, biocompatibility, and toxicity.

Nanoparticles' binding, pharmacology, and uptake properties, for example, will be monitored by common cell and molecular biology methods, such as ELISA and fluorescence microscopy. Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) will also be used as tools to observe the particle's interaction with cellular-level components. Electron microscopy, chromatography, and electrophoresis protocols allow the NCL to characterize the nanomaterial's blood contact properties, such as opsonization and macrophage phagocytosis as well as pinocytosis and uptake by nonphagocytic cells.

Also included in the in vitro characterization is a thorough examination of the nanoparticle's therapeutic and/or diagnostic functionality. For example, particles with imaging modalities will be examined for their signal intensity (i.e., signal-to-noise ratio); nanotechnology strategies that incorporate therapeutic or preventive agents will be characterized for their drug-release kinetics and ability to cross biological barriers. A nonexhaustive list of equipment used for the in vitro phase is shown in Table 1.

Table 1. Characteristic Properties, Assays, and Instrumentation

PROPERTY	ASSAY/INSTRUMENTATION
Binding and pharmacology	Enzyme-Linked Immunosorbent Assay, Flow Cytometry Fluorescence Microscopy, Surface Plasmon Resonance, Liquid Scintillation Counter
Blood contact	Chromatography, High Performance Liquid Chromatography, Gel Electrophoresis
Cellular uptake	Fluorescence Microscopy, Scanning Electron Microscopy, Electrophoresis
Toxicity, in vitro absorption, distribution, metabolism, and excretion	Microscopy, Spectroscopy, High Performance Liquid Chromatography, Liquid Scintillation, Electrophoresis

In vitro models can also serve as a gross approximation of a nanomaterial's absorption, distribution, metabolism, excretion, and toxicity (ADME/Tox) properties. For example, an initial assessment of acute toxicity can be conducted using hepatic microsomes, primary bone marrow cultures (GM-CFU), or mitochondrial toxicity assays. Other cellular assays to monitor apoptosis and cytotoxicity are now commonplace. As an example of pharmacokinetic characterization, release curves from nanoparticles with drug delivery strategies will be obtained and then assessed against other standardized release models, such as insulin.

In Vitro Diagnostics (clinical work-up)

For products that are intended to be primary diagnostics either for use in conjunction with a therapeutic or for stand-alone use, the new test should be analytically and clinically well established and should be studied in the intended use population in a manner that allows the product to be used for clinical diagnostic use. Of particular importance is establishing how well the new nanotechnology-based diagnostic performs at discriminating between true versus false positive and negative results. Table 2 lists properties that are relevant to diagnostic nanodevices.

In Vivo Characterization

The primary goal of the in vivo characterization is to elucidate the nanomaterials' safety, efficacy, and toxicokinetic properties in animal models. As is the case with any new chemical entity (NCE), these properties and other ADME data must be obtained prior to transitioning the nanoparticles to clinical applications. This phase will leverage the plethora of knowledge and protocols used to characterize drugs and devices in vivo.

Table 2. Characteristic Properties of Nanodevices for Diagnostic Applications

PROPERTY	DIAGNOSTIC APPLICATIONS
Accuracy	Does the method measure an established true value of a new or old analyte?
Precision	Does the method provide consistent measurements over time and place?
Analytical sensitivity	How low is analytical detection?
Analytical specificity	What interferes with results causing false positives and negatives?
Clinical sensitivity	How well does the test identify patients with the marker or disease process of interest?

Animal studies conducted under the in vivo phase for the study of nanoparticles will be in support of the FDA's Guidance for Industry, *Single Dose Acute Toxicity Testing for Pharmaceuticals* (http://www.fda.gov/cder/guidance/pt1.pdf). The nanoparticle will be administered to animals to identify (1) doses causing no adverse effect and (2) doses causing life-threatening toxicity. The information obtained from these tests will provide preliminary identification of target organs of acute toxicity and may aid in the selection of starting doses for Phase I human trials. Preliminary data on the nanoparticle ADME profile will also be obtained in this phase. In vivo studies will characterize the nanoparticle absorption, pharmacokinetics, serum half-life, protein binding, tissue distribution/accumulation, enzyme induction or inhibition, metabolism characteristics and metabolites, and excretion pattern.

Studies conducted in the in vivo phase for diagnostic nanodevices should support the following applicable guidances:

- *Multiplex Tests for Heritable DNA Markers, Mutations and Expression Patterns* (http://www.fda.gov/cdrh/oivd/guidance/1210.html)
- *Guidance for Submission of Tumor Marker Premarket Notifications* (http://www.fda.gov/cdrh/ode/tumor821.html)
- *Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests* (http://www.fda.gov/cdrh/osb/guidance/1428.html)

Given the multifunctional potential of nanoparticles, the in vivo characterization phase will also include an assessment of the strategy's targeting and/or imaging capabilities. Targeting will be assessed, for example, by comparing a nanoparticle distribution profile with a non-targeting nanoparticle from the same class. For those particles used with imaging modalities, the signal enhancement will be monitored using the appropriate magnetic resonance, ultrasound, optical, positron emission tomography imaging instrumentation. The NCL will actively collaborate with NCI's Cancer Imaging Program (CIP) to facilitate and harmonize the NCL studies with imaging strategies to be used in clinical trials.

NCI's Developmental Therapeutics Program (DTP) is an example of an in vivo program already in place at NCI-Frederick that can augment the NCL programs. DTP accepts candidate drugs from intramural and extramural investigators and then subjects these compounds to an extensive series of animal studies. These studies include determining a drug's maximum tolerated dose (MTD), its biological effective dose (BED), its toxicity to cardio-, hematopoietic, neurological, and nephritic tissues, and its efficacy in hollow-fiber protocols and xenograph implant models. The NCL will attempt to leverage DTP's protocols when resources permit but may also outsource the in vivo animal studies when demand and schedule warrant.

Another NCI program that conducts pre-clinical studies using animal models is the Development of Clinical Imaging Drugs and Enhancers (DCIDE) program administered by the Cancer Imaging Program. DCIDE is a competitive program to expedite and facilitate the development of promising investigational imaging enhancers (contrast agents) or molecular probes from the laboratory to IND status. The DCIDE program provides pre-clinical pharmacokinetics, dosimetry, and imaging feasibility and provides assistance with regulatory affairs for IND filing. Through its ongoing collaboration with CIP, the NCL will leverage DCIDE's expertise, personnel, and other resources whenever opportunity permits.

In addition to capitalizing on these existing animal protocols, early efforts at the NCL will also focus on standardizing the analytical and histopathological methods that are relevant, and perhaps unique, to nanoparticles. For example, several pre-clinical studies suggest a key role for macrophages in clearing nanoparticles from the blood. Similarly, a growing number of reports implicate the kidneys – rather than the liver – as the primary tissue responsible for excreting nanoparticles. Special attention will therefore be applied to standardizing assays associated with these components of the reticuloendothelial system (RES).

2. Facilitate the Clinical Development and Regulatory Review of Nanomaterials for Cancer Clinical Trials

In order to accelerate the transition of basic nanotechnology research to clinical applications, the NCL must also work closely with regulatory bodies, primarily the FDA, as it assists industry in navigating through pre-clinical tests and clinical trials. The FDA refers to this multidimensional product development and evaluation in terms of "critical path" and "critical path research." The former refers to the path from discovery or design concept through clinical evaluation to widespread clinical application; the latter is directed toward improving the product development process itself by establishing new evaluation tools. The NCL seeks to facilitate both the critical path itself and the development of critical path evaluative tools for medical product development.

In support of the critical path, the NCL will perform the pre-clinical characterization of nanomaterials intended for clinical trials. The rigorous and thorough analytical cascade used by NCL will contribute to the **scientific quality of data** submitted in the IND/IDE application package; the lack thereof is the major cause of delays in IND/IDE approval. More specifically, the NCL will generate quality data in support of paragraphs (7) "*Chemistry, manufacturing, and control information*" and (8) "*Pharmacology and toxicology information*" in 21 CFR 312.23, "*IND Content and Format*." Relevant to the multidimensional critical path (Figure 3), the NCL will assess safety through the in vivo portion of the analytical cascade. It will also address medical utility during the in vitro characterization and by developing modeling tools that help engineer and predict effectiveness of nanomaterials. Similarly, it will address scale-up and manufacturability in the physical characterization phase, by virtue of its close association with NIST.

One mechanism for the enhanced relationship between the NCL and FDA is already in place with the NCI/FDA Interagency Oncology Task Force (IOTF). The IOTF is an interagency working group representing the leadership of NCI and FDA and enabling efficient sharing of knowledge and resources to facilitate the development of new cancer drugs and speed their delivery to patients. A nanotechnology subcommittee to the IOTF has been formed to address issues related to using nanotechnology in cancer therapies and diagnostics. By interfacing with these working groups, the NCL will gain valuable insight into the regulatory review process, affording the NCL an ongoing opportunity to improve the analytical cascade on the basis of inputs from the FDA.

The relationship with the FDA is also crucial for NCL interaction with industry. Industry presently assumes significant risk in R&D for nanomaterials intended for clinical applications; the regulatory guidelines for nanomaterials are presently undefined. A standardized analytical cascade, developed in collaboration with NIST and FDA, is intended to "incentivize" industry to submit nanomaterials to the NCL for characterization, thereby reducing the high risks associated with regulatory approval. FDA itself, as a result of changes introduced by the Modernization Act of 1997, has increased flexibility in classifying new medical devices (including diagnostics), a technique called de novo classification. The FDA also has a broadened tool

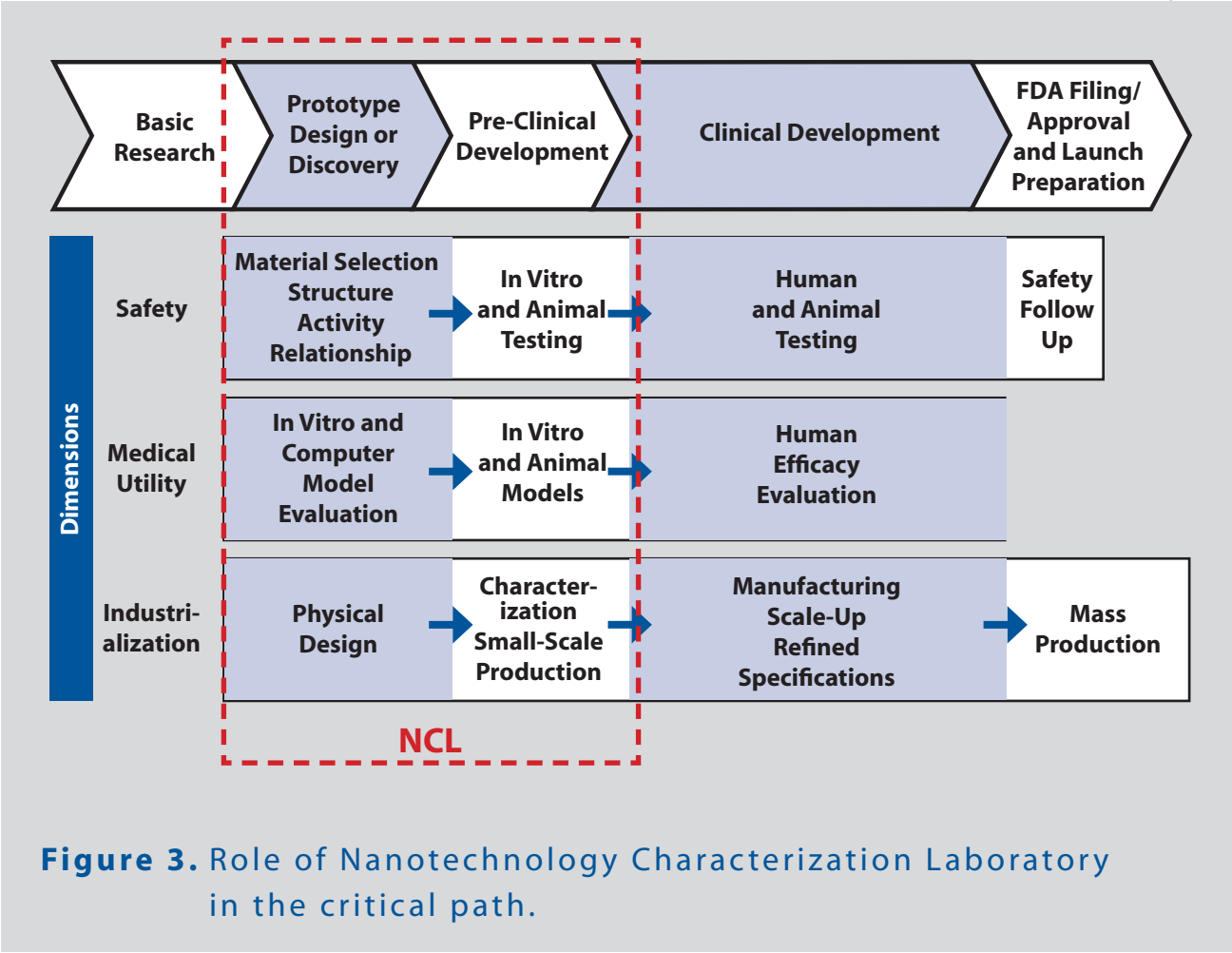

Figure 3. Role of Nanotechnology Characterization Laboratory in the critical path.

Adapted from Challenge and Opportunity on the Critical Path to New Medical Products (http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html)

box of regulatory tools, including modular PMAs, special and abbreviated 510(k)s, real-time reviews, and expedited reviews.

It is also anticipated that much of NCL's pre-clinical characterization will be amenable to the use of Drug Master Files (DMF), a submission to the FDA that permits other users to reference the study (see 21 CFR 314.420). The NCL, through the NCI, could therefore submit core nanoparticle analysis and characterization results to a DMF. Subsequent nanotechnology strategies that rely on that core nanoparticle (e.g., dendrimers) could then reference the DMF in their INDs.

3. Identify and Characterize Critical Parameters Related to Absorption, Distribution, Metabolism, Excretion, and Toxicity Profiles of Nanomaterials Using Animal Models

The analytical cascade detailed above is structured to characterize specific nanotechnology strategies that are submitted to the NCL. Concurrent with that effort will be research directed at elucidating the critical parameters that influence nanomaterials' compatibility and effectiveness in biological systems. For instance, a growing body of evidence implicates nanomaterials' size, surface chemistry, fluid dynamics, and hydrophilicity as key parameters contributing to their distribution and excretion. By determining the influence of each of these parameters (i.e., the partial derivative), the NCL will work toward a better understanding of structure activity relationships (i.e., total derivative). A systematic characterization of these parameters' influence on in vitro/in vivo ADME/Tox profiles will provide empirical data to engineering and predictive models. These modeling tools may predict and recommend functionalization and structural improvements, which can then be incorporated into the next iteration of nanomaterials submitted to the NCL (Figure 4).

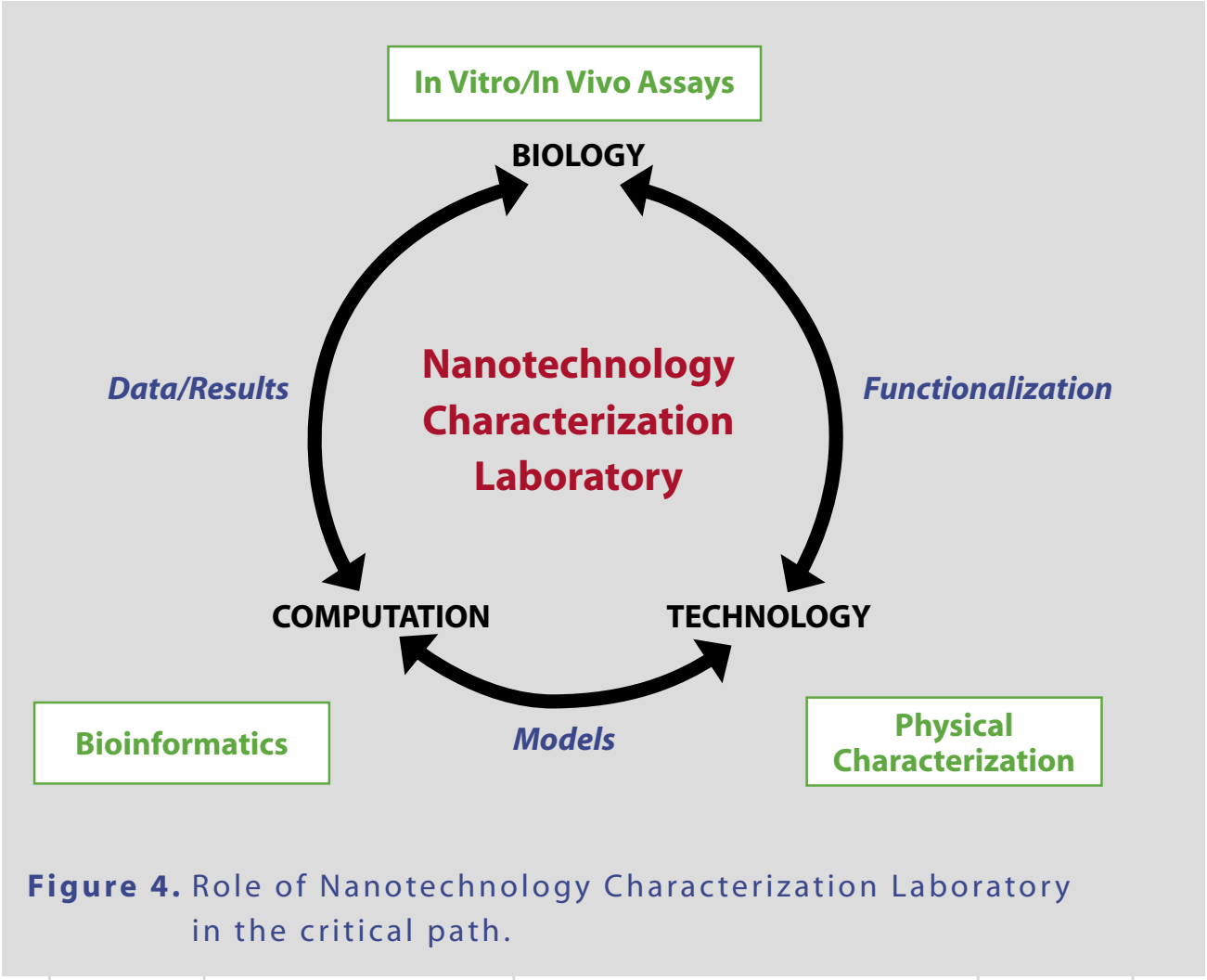

Figure 4. Role of Nanotechnology Characterization Laboratory in the critical path.

4. Examine the Biological and Functional Characteristics of Multicomponent/Combinatorial Aspects of Nanoscaled Therapeutic, Molecular and Clinical Diagnostics, and Detection Platforms

By virtue of their multifunctional capabilities, nanoscale devices can include targeting agents, diagnostic components, and therapeutic payloads all within the same platform. These "smart" nanotherapeutics may provide clinicians with the ability to tailor nanoparticles to target specific tissues, release anticancer drugs or deliver in a timed manner, and monitor efficacy in near real time. The NCL will facilitate the advancement of multifunctional nanoscaled platforms primarily by promoting collaborations between otherwise unassociated researchers. Looking to future capabilities, the NCL may conduct its own combinatorial studies to take advantage of the multifunctional potential of nanoparticles. Once a core technology is characterized, for example, the NCL may be in the best position to exploit the modular aspects of nanotechnology's targeting, imaging, therapeutic, and diagnostic components. Although the NCL seeks to enable the larger nanotechnology community to conduct basic research, this intramural approach may be pursued if it is viewed to be in the best interests of the government.

The list of conceivable combinatorial nanodevices is immense and grows exponentially with each new targeting ligand or novel nanomaterial. An exhaustive characterization of each of these combinations is obviously beyond the scope and resources of the NCL. The NCL will therefore work closely with regulatory entities to identify taxonomies of nanomaterials with similar ADME/Tox profiles. As corporate understanding of nanomaterials' interaction and compatibility with biological systems matures, redundant characterization studies on related categories of nanodevices could be reduced. Additionally, the NCL – in collaboration with the Advanced BioComputing Center (ABCC) at NCI-Frederick, NIST, and FDA – will develop predictive and engineering modeling tools that may eventually offer in silico alternatives to some aspects of the analytical cascade.

5. Engage and Facilitate Academic and Industrial-Based Knowledge Sharing of Nanomaterial Performance Data and Behavior Resulting From Pre-Clinical Testing (i.e., Physical Characterization, In Vitro Testing, and In Vivo Pharmaco- and Toxicokinetics)

The NCL is intended to serve as a nexus for cross-disciplinary research, development, and clinical applications of nanotechnology. The NCL will disclose its findings to the scientific community and the public through full use of journal publications, scientific conferences, public forums, the Internet, and press releases. Care will be taken, however, to ensure that proprietary information and materials disclosed to the NCL by industry are protected in accordance with the terms of agreement (e.g., Material Transfer Agreement).

The primary output of NCL's analytical cascade will be data and information related to nanomaterials' interaction and compatibility with biological systems. NCL's output will be provided to the originating investigator, and will include all aspects of the analytical cascade for support of an investigator-held IND application and subsequent clinical trials. Depending on the pre-negotiated agreement with the investigator, the NCL may wait up to 60 days prior to making NCL data available to the public domain. This delay allows for the submitting investigator/vendor to file the relevant patent application to further secure their intellectual property (IP). The emphasis of the NCL, however, is to serve as a nexus for transdisciplinary research, development, and clinical applications of nanotechnology. Information, knowledge, tools, and methods gleaned from the NCL's analytical cascade must therefore be made readily available to material scientists, engineers, modelers, regulatory bodies, and intramural and extramural cancer researchers.

As mentioned in the above section, the NCL will establish and maintain models, tools, and databases of information generated by the analytical cascade. This knowledge base will be made available in the public domain with the intent of capitalizing on the "collective" approach and efforts. The Cancer Biomedical Informatics Grid (caBIG) is an example of such a mechanism and serves as a model for disseminating data in a standardized format. Resources provided to the scientific community will include:

- Assay data (e.g., pharmacokinetic properties, toxicities, fluid dynamics, and general compatibility with biological systems) and links to publications detailing these results.
- Theoretical, detailed, systems, engineering, and statistical models used in the predictions, comparisons, and analyses of the data from nanoparticles/device characterization.
- Links to model descriptions, assumptions, validations, expert users, and vendors.
- Links to scientific and clinical users of those models, whether individuals, institutions, agencies, universities, or companies.
- Cross-referencing and links to related research, results, and publications contained in other databases.

Communication between the NCL and its "customers" will also be structured to ensure requirements are met. NCL's customers are the end-users of the characterization data: cancer researchers, the FDA, and the pharmaceutical industry. As an example, the NCL management will meet with FDA representatives on at least a quarterly basis to ensure that procedures (i.e., the analytical cascade), data, and quality of nanomaterials are conducive to facilitating clinical applications. Similarly, the NCL will liaison with the nanotechnology, in vitro diagnostic, and pharmaceutical industries on a regular basis to facilitate and promote the rapid translation of this technology to market.

6. Interface With Other Nanotechnology Efforts

Cancer Research

The emphasis of the NCL on the many facets of cancer research enables it to serve as a nexus for transdisciplinary research, development, and clinical applications of nanotechnology. As annotated above, the NCL intends to provide resources, knowledge, tools, and methods for cancer researchers. It does not seek to duplicate the efforts of established and emerging programs by academia, industry, or government programs in nanotechnology or to intrude on the domain of other programs. Rather, it seeks to partner with these programs. To this end, the NCL will collaborate wherever possible with other government agencies, academia, and industry to leverage their resources and expertise in pursuit of common goals and to accelerate the use of nanotechnology in critical national applications to cancer.

Nanoscience and Nanotechnology

Substantial government and private investments have been made and continue to be made in nanoscience and nanotechnology:

- Through funding from the National Nanotechnology Initiative (http://www.nano.gov/) to support fundamental and applied research, establishment of multidisciplinary centers of excellence, and development of infrastructure.


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- Through private investment across industry, but primarily through the increasing investment in small businesses to bring new nanomaterials and nanotechnology products to market.
- Through the new Advanced Measurement Laboratory at NIST, created to respond to the need for advanced measurement methods and standardization in research and development. NIST also continues to work to promote development of material standards for use in support of old and cutting-edge diagnostic technology.
- Through other government agency investment, such as the Nanomedicine Roadmap Initiative (http://nihroadmap.nih.gov/nanomedicine/) at NIH to understand molecular pathways and networks and to use that knowledge to design and develop new technologies and devices to improve human health.
- Through NCI-funded intramural and extramural projects, such as those funded by the NCI Alliance for Nanotechnology in Cancer (http://nano.cancer.gov), to support development of novel technologies for noninvasive detection, diagnosis, and treatment of cancer.

Health, Safety, and the Environment

The lack of knowledge concerning the health and safety of nanomaterials may also become an obstacle to rapid implementation of nanotechnology. Although industry has long manufactured fine and ultrafine (i.e., nanoscale) particles for use in a variety of applications, the effect of those particles on human health has been studied for only a small number of materials and applications. In addition, the waste streams generated by the manufacturing and assembly processes for nanomaterials and by their disposal have generally not been subjected to detailed examination and analysis. The analytical cascades developed by the NCL can provide a preliminary measure of the effects of these materials, devices, and waste products on human safety – especially those effects related to the acute toxicological properties of nanotechnology. Elucidating the environmental and health effects and implications of nanotechnology is far beyond the scope and resources of the NCL, however. Such an effort will require national collaboration between nanotechnology research institutions, developers, and product manufacturers to formulate the appropriate assays and protocols to address this public need.


Fitting fixed to ceiling
Rockwool Rollbatt,
or equivalent
Rockwool triangular fillet
50mm

NANOTECHNOLOGY CHARACTERIZATION LABORATORY OPERATIONS

Input of Nanomaterials

The NCL's charter is to serve as a national characterization facility for nanomaterials submitted by academia, industry, and other government laboratories, i.e., intramural and extramural sources. The NCL is not structured to conduct basic material sciences research or fabricate novel nanomaterials. Nanotechnology strategies submitted to the NCL will be subjected to a standardized characterization cascade, developed in collaboration with NIST and FDA. This "collective" approach allows the NCL to leverage a knowledge base of material sciences information, characterize the material against a panel of standardized assays, and facilitate a nanomaterial's development and translation to clinical application.

The uniqueness of this structured approach is intended to be attractive to developers and producers of nanomaterials because it reduces risk and expenditure of their resources. For example, a materials scientist or engineer in academia or with a small nanotechnology firm may invent a nanodevice that has potential applications in cancer therapy and diagnostics. This researcher may have minimal expertise in biology, and likely does not have ongoing interaction with the pharmaceutical community. By submitting the nanomaterial to the NCL, the particle/device will be characterized for its compatibility with biological systems and, assuming favorable results, will become a candidate for regulatory review. Submission to the NCL's analytical cascade therefore affords universities and small businesses an entry point into pharmaceutical markets, with minimal cost and risk. When appropriate, the NCL may also reimburse scientists for their efforts or may sponsor development of nanoscaled platforms through research contracts.

Similarly, companies already involved in drug discovery would be encouraged to submit their nanoparticles and devices to the NCL because of its pre-clinical interactions with the FDA and the knowledge base generated by a community approach to commercialization of nanomaterial. One source quoted by the FDA points to errors in a material's pre-clinical characterization as a major cause of escalating costs for drug development:

> "The main causes of failure in the clinic include safety problems and lack of effectiveness: inability to predict these failures before human testing or early in clinical trials dramatically escalates costs. For example, for a pharmaceutical, a 10-percent improvement in predicting failures before clinical trials could save $100 million in development costs per drug."
>
> (Source: Boston Consulting Group as referenced in Challenge and Opportunity on the Critical Path to New Medical Products http://www.fda.gov)

Finally, companies interested in diagnostic applications would have a resource to use for supporting early development and ensuring proper grounding and links in the exploration of diagnostic nanotechniques for cancer. The NCL would be in a unique position to ensure that when a link between a diagnostic and a new nanotechnology therapeutic appears warranted, both technologies could be evaluated in a concurrent and synergistic manner.

The NCL is intended to accomplish precisely this: reduce the cost and risk associated with the development pathway by standardizing the pre-clinical efficacy and toxicity testing and facilitate the regulatory review process.

Entrance Criteria for Candidate Nanomaterials

Given the large number of candidate nanomaterials that could be submitted to the NCL for characterization, a set of entrance criteria will be applied to candidate nanotechnology strategies to aid in their selection and prioritization. Nanostrategies proposed to the NCL for characterization will be ranked according to the measure of their projected impact on clinical cancer applications and/or furthering nanotechnology's compatibility with biological systems. Specific evaluation criteria include, but are not limited to:

- Previously demonstrated efficacy in vitro and/or in animal models.
- Advantages offered by the strategy over existing cancer therapies or diagnostics.
- Previous physical characterization of the nanomaterial, such as determining purity and stability.
- The nanostrategy's manufacturing process and compatibility with scale-up.
- The material's inherent toxicity and/or environmental concerns.
- Plans or approach to transition the strategy to clinical trials (e.g., filing the follow-on IND, IDE, or pre-IDE).

Intellectual Property

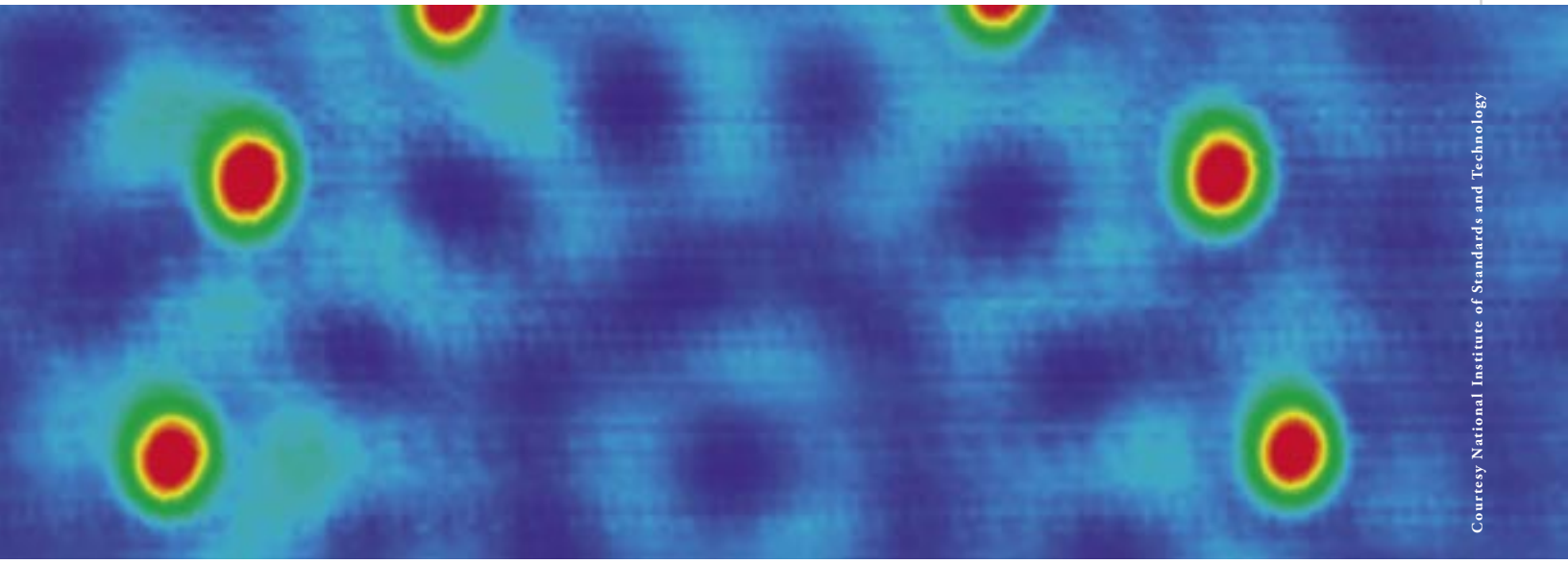
It is expected that originating parties will have taken initial steps to secure intellectual property protection before their involvement with the NCL. To share and safeguard Research Material and proprietary information, the NCL's interaction with extramural researchers and vendors will normally be conducted under a Material Transfer Agreement (MTA). The MTA permits the collaborative exchange of materials and associated information between NCL and the originating party(s) without the promise of resulting intellectual property. However, if NCI does file a patent application for technology developed at the NCL, the originating party will be given the opportunity to negotiate for a nonexclusive license under procedures set forth in 37 CFR Part 404.

By exception, the collaboration can be conducted under a Cooperative Research and Development Agreement (CRADA). Under the CRADA, the originating party is provided an exclusive or co-exclusive option to negotiate an exclusive or co-exclusive license to inventions conceived or first actually reduced to practice under the CRADA. CRADAs associated with the NCL are handled by the NCI Technology Transfer Branch. Contact information for NCI's Technology Transfer Branch can be found on the Web at http://ttb.nci.nih.gov/.

However, given the anticipated "multifunctional" aspect of resulting nanoplatforms, originating parties must appreciate that their intellectual property may be one of many components in a composite system. The product eventually used in the clinic, for example, may comprise a targeting molecule, a diagnostic tool, and a drug delivery component – each originating from a different inventor. This may require the originating party to accept a co-exclusive license and/or pursue cross-licensing with a third party(s).

Education and Training

The cross-disciplinary nature of NCL provides a unique opportunity to educate and train scientists in the field of nano-biotechnology. It is anticipated that graduate students, postdocs, and scientists from the disciplines of material science, engineering, physics, chemistry, pharmacology, toxicology, immunology, and cancer research will be able to conduct research in the NCL. Additionally, the NCL will sponsor seminars and workshops to familiarize and equip intramural and extramural researchers with nano-biotechnology protocols and capabilities.



Courtesy National Institute of Standards and Technology

MANAGEMENT AND ADMINISTRATION OF THE NANOTECHNOLOGY CHARACTERIZATION LABORATORY

The Nanotechnology Characterization Laboratory Technical Steering Committee

As stated throughout this document, the primary goal of the NCL is to facilitate the accelerated transition of basic nano-biotechnology research to clinical trials. The NCL will therefore adopt a "systems approach" model to support NCI's mission and to meet "customer" requirements.

To elaborate, the specific requirements for entry into the clinic will be defined early on in collaboration with the FDA to the fullest extent possible. The NCL's analytical cascade will then be directly linked to those guidelines. Concurrently, the NCL must get inputs from NIST and the pharmaceutical industry to ensure that the nanoparticles' characterization and fabrication are conducive to scale-up and rapid transition to industry.

To oversee these goals, the NCL will assemble a Technical Steering Committee with representatives from the supporting organizations (i.e., NCI, NIST, and FDA) and the pharmaceutical, diagnostic, and nanotechnology industries. The Technical Steering Committee will be tasked with (1) recommending and reviewing NCL's prioritization of resources, (2) monitoring NCL activities to avoid duplication of effort with other government entities, and (3) facilitating interactions with their respective organizations.

Performance Measures

On the basis of the number of staff, facilities, and supporting equipment, the NCL is anticipated to be able to receive several dozen nanoscaled particles/devices in the first year. However, because of the nanomaterials' inherent toxicity, impurity, or lack of compatibility with biological systems, only a few of these are expected to be nominated for and complete in vivo testing, i.e., the full analytical cascade. The first two phases are intended to act as a screening method for acute toxicity and/or other disqualifying properties. Assuming a 12-month timeline to complete the characterization, the NCL will subject at least six nanoscaled particles/devices to the entire analytical cascade per year. This number may increase to greater than 20 per year as the laboratory expands in personnel and resources.

Personnel

In addition to the NCL Director and support staff, the scientific disciplines represented at the NCL include immunology, pharmacology and toxicology, and biochemistry. Brief descriptions of these senior-level positions are as follows:

The **Director** coordinates and oversees the efforts of all NCL scientists and staff to develop new approaches, methodologies, and standards to characterize nanotechnology-based devices and platforms. He or she will coordinate NCL efforts with requirements from scientists and management within intramural and extramural programs at NCI and NIH, with capabilities of other NCI laboratories and with related efforts at FDA and NIST. The Director will represent the NCL and NCI at various intra- and inter-agency meetings, working groups, policy forums, and scientific conferences and will be responsible for maintaining outreach efforts with academia and industry.

The **Immunologist** will direct characterization related to the nanomaterials' interaction with components of the immune system. In the tissue culture and in vitro environment, this person will develop and perform assays to monitor recognition and phagocytosis by leukocytes, opsonization, and other blood contact properties. The Immunologist will also perform these assays for animal studies, characterizing the materials' effect on hematopoietic tissues and the RES, and monitor any other acute/adverse effects related to the immune system.

The **Toxicologist** will develop and perform assays that serve as pre-clinical surrogates for toxicity. In the laboratory, these assays will include monitoring for apoptosis and cytotoxicity in hepatic and kidney cells, and identifying metabolic products and pathways. In animal models, this scientist will collaborate with SAIC-Frederick's histopathologist to fully characterize the particle's toxicokinetic properties and assist the NCL's scientists with ADME/Tox, mass balance, and other pharmacodynamic protocols.

The **Biochemist** will develop and conduct assays and protocols that support the material sciences aspects of the NCL. For instance, this scientist will develop and oversee protocols that deal with the physical characterization phase of the analytical cascade, such as chromatography, electron microscopy, and elemental composition and purity. When applicable, the Biochemist may modify and optimize the nanoparticle's surface chemistry.

Relationship to SAIC-Frederick

The NCL is a government-owned, contractor-operated (GOCO) facility under NCI's federally funded research and development center (FFRDC) and will fall under NCI-Frederick's Operations and Technical Support (OTS) contract. SAIC-Frederick, Inc., a subsidiary of SAIC, is the OTS contractor for NCI-Frederick. The mission of SAIC-Frederick, Inc., is to provide scientific, technical, management, administrative, and logistical support to NIH intramural laboratory research and development related to the causes of and cures for cancer and AIDS.

SAIC-Frederick, Inc., is one of four related NCI contracts on site and serves as the infrastructure support for the entire center. The contract is the largest single research contract awarded by the U.S. Department of Health and Human Services and is the Department's only government-owned, contractor-operated facility contract. SAIC-Frederick, Inc., employs more than 1,500 staff including scientists, research assistants, technicians, engineers, and administrative, maintenance, and support personnel.

SAIC-Frederick operates under a variety of regulatory, performance, and quality standards. These include:

- SAIC-Frederick operates the NCI's Biopharmaceutical Development Program and the NIAID/ Vaccine Research Center's Vaccine Pilot Plant. Both programs manufacture pharmaceuticals for use in human clinical trials. These products are manufactured in accordance with FDA requirements for Current Good Manufacturing Practices 21CFR Chapter 1 Parts 210 and 211 and Biological Products Requirements 21 CFR Chapter 1 Parts 600 and 610 .

- SAIC-Frederick clinical testing laboratories in accordance with 42 CFR Part 493 "Clinical Laboratory Improvement Amendments (CLIA)."
- SAIC-Frederick research laboratories are operated in accordance with 21 CFR Part 58 "Good Laboratory Practice for Nonclinical Laboratory Studies."
- NCI-Frederick laboratory animal science programs, operated by SAIC-Frederick, are AAALAC accredited (Association for Assessment and Accreditation of Laboratory Animal Care) and operated in accordance with the Guide for the Care and Use of Laboratory Animals and Public Health Service Policies. NCI-Frederick maintains an Assurance through the NIH Office of Animal Care and Use.

Facilities

In addition to collaborative resources located at NIST, the NCL laboratory facilities will initially be located on the second floor of Building 469 on the NCI-Frederick campus. This facility is adjacent to, and will integrate with, other relevant NCI-Frederick laboratories such as the electron microscopy laboratory and the animal care facility. The laboratory in Building 469 is outfitted with a tissue culture room, an isotope laboratory, two research bays, a cold room, a chromatography and electrophoresis area, and open floor space for freestanding instrumentation and equipment. This facility will support up to 10 personnel.

Annexes 1, 2, 3

Annex 1: The Application Process

Annex 2: Nanotechnology Characterization Laboratory's Material Transfer Agreement

Annex 3: Interaction Between the Nanotechnology Characterization Laboratory and Nanotechnology Providers

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