ANNEX 1

NATIONAL CANCER INSTITUTE
NANOTECHNOLOGY CHARACTERIZATION LABORATORY
THE APPLICATION PROCESS

Solicitation of Nanotechnology Strategies for Cancer Research

The Nanotechnology Characterization Laboratory (NCL) performs pre-clinical efficacy and toxicity testing of nanoparticles and facilitates regulatory review of nanotechnology intended for cancer therapies and diagnostics. The NCL is a resource that enables researchers in academia, industry, and government to transition their nanotechnology strategies to clinical applications. The NCL provides critical infrastructure and characterization services to these nanomaterial providers but does not fund research grants.

As part of its assay cascade, the NCL will characterize nanoparticles' physical attributes, their in vitro biological properties, and their in vivo compatibility using animal models. The time required to characterize nanomaterial from receipt through the in vivo phase is anticipated to be 1 year. Proposed nanotechnology materials and strategies submitted to the NCL will be evaluated according to the measure of their projected impact on clinical cancer applications and/or furthering nanotechnology's compatibility with biological systems. If a nanotechnology strategy/material is selected for characterization, NCL's services will be provided at no cost to the submitting investigator.

The primary output of NCL's assay cascade will be data and information related to the nanoparticles' interaction and compatibility with biological systems. These data will be provided to the originating investigator for support of an investigator-held IND application and subsequent clinical trials. Submission to the NCL's assay cascade therefore affords "nano-bio" researchers an entry point into the clinical realm, with significantly reduced cost and risk.

Submission to the NCL

The NCL solicits nanotechnology strategies from academia, industry, and government. Desired nanotechnology proposals include, but are not limited to, strategies that incorporate image contrast agents, cancer therapeutics, and/or targeting receptors or ligands. Given the large number of candidate strategies/nanomaterials that could be submitted to the NCL for characterization, a set of evaluation criteria will be applied to proposed nanotechnology strategies to aid in their selection and prioritization. A panel consisting of scientists from NCL, NCI, the pharmaceutical industry, NIST, FDA, and the nanotechnology industry will review and evaluate the proposals.

The application process is conducted in two parts (Table 1); Part I is a three- to four-page white paper that describes the strategy/concept; Part II is a full proposal. The initial white paper is intended to give NCL reviewers an overview of the strategy, without requiring investigators to prepare costly, time-consuming proposals. Researchers with white papers (i.e., nanotechnology strategies) deemed to be of interest to NCL reviewers will be asked to submit full proposals for Part II.

The primary evaluation criterion for white papers in Part I is the strategy's previously demonstrated capability in a biological system relevant to cancer research. For the purposes of this application, a "biological system" is defined as an in vitro or in vivo system that uses biologically relevant molecules. The NCL appreciates that biologically relevant data for proposed nanotechnology strategies may be preliminary and limited because of the novelty of this field. However, white papers that address only the "material sciences" aspects of nanotechnology are not desired.

Table 1.

Application	Intention	Size of Application	Evaluation Criteria
Part I	Overview of nanotechnology strategy	White paper: 3-4 pages (no smaller than 12 point type)	Demonstrated efficacy in a biological system (in vitro or in vivo)
Part II	Full proposal	20-30 pages	1. Part I criterion 2. Anticipated impact of strategy on clinical cancer therapeutics and/or diagnostics 3. Previous characterization of material 4. Manufacturing process; compatibility with scale-up 5. Inherent toxicity of nanotechnology concept 6. Plan or strategy to transition the concept to clinical use

The six evaluation criteria are listed below. For Part I of the application (i.e., white paper), submitters are required to address only evaluation criterion 1. Applicants requested to submit a full proposal for Part II must address all six criteria.

Evaluation Criteria

1. Demonstrated Efficacy in a Biological System (In Vitro or In Vivo)

Give a detailed overview of the nanotechnology strategy: what it is, what it does, how it works. Provide detailed descriptions of the nanomaterial's physical properties, chemical structure, and stability. Present and discuss preliminary data and the materials and methods used. Address the inherent strengths and limitations of the strategy (e.g., anticipated in vivo half-life of the material, toxicity, potential to elicit an immune response, etc.).

2. Anticipated Impact of Strategy on Clinical Cancer Therapeutics and/or Diagnostics

Describe the projected clinical use of the material and the basic biological mechanisms of action. What is the strategy's "value added" when compared to existing therapeutics and diagnostics? If the strategy has benefits due to targeting and/or specificity, discuss the specific underlying mechanisms and include data to support these claims. Describe any measured ADME/Tox, pharmacokinetic parameters, and any analyses comparing the results to current therapeutics or devices.

3. Previous Characterization of Material

The material providers need to supply detailed information on assays previously used to characterize the material and the reproducibility of those assays. As part of its assay cascade, the NCL will provide an initial screening to determine the variability of basic physical and chemical parameters of the material provided. If the variability is so large that further physical and biological assays will not provide meaningful data, the assay cascade will be discontinued for that strategy. The demonstrated ability to control the physical parameters of the material will therefore be a weighted evaluation criterion.

4. Manufacturing Process; Compatibility With Scale-Up

Briefly describe the manufacturing process and steps used during purification. Discuss impurities that may be present in the final product. Provide information on the cumulative amount of nanomaterial (e.g., milligram, gram, or kilogram) produced to date, and the batch-to-batch variability. Discuss potential obstacles associated with producing enough material for preliminary pharmacology and toxicology studies. Is a reference standard for the nanomaterial available?

5. Inherent Toxicity of Nanotechnology Concept

Include information on relevant safety and/or environmental issues related to the production, purification, and/or handling of the nanomaterial. For example, if the nanomaterial contains a known toxic compound, discuss how the strategy overcomes or mitigates potential adverse health effects. If known, discuss supporting reagents/reactants/solvents that may be used in scale-up production, as well as waste streams that might be generated in the manufacturing process.

6. Plan or Strategy To Transition the Concept to Clinical Use

Information related to teaming with industry, academic, or other government partners in the translation effort is of interest to the NCL. If applicable, describe steps previously taken toward translation of the strategy/nanomaterial to clinical use. Discuss possible sponsors for future studies or trials and/or arrangements with commercial production firms. Discuss intellectual property issues related to the material, especially if the material utilizes licenses or represents an improvement or modification of an existing material or production process. If applicable, a brief summary of similar or closely related antecedents or approaches to the submitted strategy/nanomaterial should be provided.

Submission Dates and Procedures

White Paper Application (Part I)

Part I white papers are accepted quarterly, with due dates on the first business day of March, June, September, and December. Phase I white papers should be submitted using the following form: NCL White Paper Application. (Additional figures and/or tables may be added to the last page.) Submit the completed application by one of the following methods:

Mailing Address: **Nanotechnology Characterization Laboratory**
Attn: Part I Proposal
1050 Boyles Street
Bldg 469, Room 246
Frederick, MD 21702-1201

Email: NCLwp@ncifcrf.gov

Web: http://ncl.ncifcrf.gov/wp/upload.asp

White papers will be reviewed within 45 days.

Full Proposal (Part II)

Applicants requested by the NCL to submit a full proposal for Part II need to mail six hardcopies and one digital copy of the proposal, within 45 days of request, to:

Mailing Address: **Nanotechnology Characterization Laboratory**
Attn: Part II Proposal
1050 Boyles Street
Bldg 469, Room 246
Frederick, MD 21702-1201