Notice of Limited Competition Request for Applications: Nanomedicine Development Centers **(NOT-RM-05-010)**

This "Notice of Limited Competition" (http://grants2.nih.gov/grants/guide/notice-files/NOT-RM-05-010.html) was published in the NIH Guide for Grants and Contracts on April 13, 2005 indicating that eligibility to apply for a Nanomedicine Development Center (NDC) is limited to recipients of Concept Development Awards that were issued in response to RFA-RM-04-018, "Nanomedicine Center Concept Development Awards" (http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-04-018.html).

A novel process was undertaken for planning and developing the following request for applications for Nanomedicine Development Center awards. This process and timetable is described in "Part 2 – Solicitation of the Concept Development Memo (CDM)" in the aforementioned RFA.

A second solicitation (RFA) for additional Nanomedicine Development Centers will be issued in FY2006 and will be an open competition. The content of the FY2006 RFA is expected to be similar to the text contained herein. When the FY2006 RFA is issued, it will appear in the NIH Guide to Grants and Contracts, and a notice will be broadcast using the Nanomedicine email listserve. You can sign up for this email list at http://nihroadmap.nih.gov/nanomedicine/index.asp

This RFA is unique in form and requirements, and unlike traditional NIH RFAs, it is written specifically for the recipients of Concept Development Awards (PN1) who participated in the planning process and program development.

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PART I. Introduction and Background

NIH Vision for Nanomedicine

Nanomedicine is one of nine major initiatives included in the NIH Roadmap for Medical Research in the 21st Century. The initiatives of the NIH Roadmap address major opportunities and gaps in biomedical research that no single institute at NIH could tackle alone. To stimulate the emerging field of Nanomedicine, the NIH Roadmap Nanomedicine project team engaged the extramural biomedical research community to develop concepts and a novel process for awarding Nanomedicine Development Centers (NDC). The NIH vision is conceived as a ten year[1] plan to:

- Characterize quantitatively the physical and chemical properties of known molecules and nanomachinery in cells.
    - Determine what measurements and analytical and computational tools are needed to understand biological system design at the molecular level with the precision required to interface with nanotechnology.
    - Develop quantitative analyses of biomolecules and their interrelationships.
    - Understand biological design, by measuring physical parameters such as force, subunit stoichiometry, kinetics, affinity, materials requirements and properties, energy utilization and transduction in ways that are compatible with possible interface to nanotechnology.
- Understand the engineering principles used in living cells to synthesize or assemble molecules, molecular complexes, organelles, cells, and tissues.
    - Develop, refine, and apply measurements to biological systems to elucidate design principles.
    - Develop standards, a lexicon of engineering terms, definitions, specifications, and data systems applicable to biological processes and structures.
    - Use knowledge of properties and design principles to develop new technologies, and to engineer devices and hybrid structures for repairing tissues as well as preventing and curing disease.

The scientific basis for this initiative is described in the original RFA for planning awards, available at http://grants1.nih.gov/grants/guide/rfa-files/RFA-RM-04-018.html.

[1] The matrix describing the Nanomedicine Roadmap Initiative concept is included as an appendix to this RFA and was provided to participants at the March 10, 2005 CDP grantee meeting.

Funds Available

The schedule for funding the Nanomedicine Initiative (Approximate Total Costs):

2005 $6 million
2006 $12 million (including $6 million added for new centers)
2007 $12 million
2008 $25 million
2009 $25 million

It is our expectation that 3 or 4 centers will be funded in 2005. An RFA similar to this one will be issued for FY2006 when 3 or 4 additional centers will be awarded. The centers and network will continue to evolve based on the experience of the funded centers and project team; the CDM/CDP planning process will not be repeated. The requirements and conditions for FY2006 NDCs will be similar to those for the FY2005 NDCs, and all NDCs will be incorporated into the same network.

The increase of available funds in FY2008 and 2009 is expected to be used to expand the operations of the centers funded in FY2005 and 2006. However, NIH and network oversight will remain flexible in allocating resources where they can be utilized most effectively in order to provide for the changing needs of the Nanomedicine program. For example, not every center will necessarily receive increases, and it is possible that additional solicitations for applications may be offered to meet changing needs of the network. See below, PART IV, "Award Management and Administrative Information" (page 19) for more specific funds management information.

As previously mentioned, the scientific vision of the Nanomedicine Roadmap Initiative was conceived as a ten year plan. NIH Roadmap funding plans have been established only through 2009. It is anticipated that each Roadmap initiative will be evaluated for continuation after that date, and we expect that successful implementation of the Nanomedicine Initiative will lead to continued support in the future. Awards will be 5 years, and it is anticipated that if the Nanomedicine initiative continues for 10 years, awarded centers will be able to re-apply for an additional 5 year period.

PART II. Instructions for Preparing your NDC Application

You must use the PHS 398 Application Forms. To prepare your NDC application you will need to refer to the instructions below as well as the PHS 398 instructions. Many aspects of the NDC application instructions differ significantly from standard NIH applications, so instructions found herein supersede the PHS 398 instructions. If not specifically addressed below, follow the PHS 398 instructions.

The complete PHS 398 instructions and form pages are found at
http://grants.nih.gov/grants/funding/phs398/phs398.html

Administrative Information

Description, Key Personnel, Biographical Sketch, and Resources and Environment

Refer to p. 23-30 of PHS 398 Instructions, except Key personnel must appear in a separate table (see below).

Budget

Provide detailed budgets; do not use the modular budget format.

Funds are available ($6 million total costs annually) to support three or four centers for up to five years beginning in FY2005. However, 15% of the total Nanomedicine program funds will be set-aside for allocation within the network as opportunities or needs arise. Consequently, when determining your budget, you must assume a fixed base amount of funds available that does not include set-aside funds. For an example of funds allocation, refer to the table in PART IV "Award Management and Administrative Information: Model for Resource Allocation" (page 21).

You may submit plans for scale-up in FY2008 and FY2009, but no firm commitments will be made by NIH in the original award. A detailed request will be required in FY2007 that will be subject to additional review by NIH staff and possibly an outside review panel.

There are no specific budgetary requirements for the percentage of work required in the funded institution relative to consortia or subcontracts.

Other Support

Other support information must be submitted with the application. Scientific Program and Grants Management staff will review this information before award to ensure the following:

- Sufficient levels of effort are committed to the project.
- There is no scientific, budgetary, or commitment overlap.
- Only funds necessary to the approved project are included in the award.

Additional information regarding other support can be found in the PHS 398 application kit and the NIH Grants Policy Statement http://grants.nih.gov/grants/funding/phs398/phs398.html and http://grants.nih.gov/grants/policy/nihgps_2003/index.htm.

Page Limits

Research Plan (A-C, see below):	**35**
Biographical Sketches:	**4 pages/person** (refer to the 398 instructions)
Organization and Network:	**5**
Assurances (G-I, see below):	**none**
Appendix:	**10 items**

No more than 10 publications limited to accepted manuscripts **not already in print or on-line** as of the date of submission. **Appendix hard copies will not be accepted. Appendix material must be included on the CD (see above, p. 10).** Each reviewer and staff member will receive a copy of your CD with your application PDF and Appendix materials. Any figures or photos must be included as high quality images in those PDF files. No printed copies will be sent to the review team.

Research Plan

***** Applications will not be reviewed unless each lettered section heading (A – H) and appropriate contents are included in your application:**

A. Introduction, Vision, Background, and Significance

Your NDC application must be self-contained. Although some reviewers will have participated in earlier activities of this initiative, additional reviewers with required technical expertise will be recruited to evaluate these applications. They will not be given copies of your CDM or CDP. You should incorporate the following information in this section:

- Theme of the proposed Nanomedicine Development Center
- Model system: why is it a good one in which to develop new tools and concepts?
- What is the physiological or medical relevance of the system?
- What information is lacking for a quantitative description of the system?
- What tools are in place and what additional ones will be required to achieve the aims?
- How will you generalize the new tools and concepts to other systems?
- What biological design principles will be elucidated?

B. Published Work, Studies in Progress, and Research Expertise

Summarize the research for which you are currently funded (or research that is pending through conventional mechanisms) – its rationale, methods and anticipated endpoints. This includes the biological goals, the data sets, and the tools that you are currently developing. Describe your team's expertise and include any relevant information to demonstrate your research team's capabilities, interactions, and collaborations. You should refer to your Table of Key Personnel where appropriate (see page 11; E. Center Structure).

C. New Studies and New Directions

The NIH Roadmap Nanomedicine Initiative is conceived as a ten-year plan working toward engineering devices or molecular components for human health and medical practice. Although your NDC application will request funds for a five year period, it is important to maintain the perspective that the vision and goals of the program are geared to at least a ten year development period. In five years, you are not expected to complete the entire sequence from developing new tools, making novel measurements and developing engineering-level understanding of biomolecular systems, to ultimately developing novel medical devices. When describing your studies, refer to your expectations about where you realistically expect to be after five and ten years (the five-year timeline will of course be presented in much more detail and linked to the research plan).

This is the section where your bold new initiatives should be discussed. How are they different from ongoing projects? What novel endpoints would be achieved in comparison with the studies described in the previous section? Describe here the new studies that will be initiated because of the unique team that has coalesced. Specify the levels of risk of the proposed work, and justify those statements.

The following may help to guide your thinking on issues to address in this section:

- What data/data types are missing, either because we had not realized they were needed (because we were not asking the question from the perspective of system design) or because we do not have the tools to measure them? Which of these are your initial targets; why have you chosen them?

- As previously stated, the purpose of the NDC is not to supplement or accelerate ongoing research. That research will continue, and the data sets, which will complement those acquired under the NDC, will become available in the near future. You may think of the NDC as a way to develop the tools and approaches you will need five years from now. However, initial work at your NDC may depend on a few key issues related to your ongoing work. If so, identify those issues and justify why you must use NDC funding to accelerate that research so that you will be in a position to proceed with the goals that are central to the NDC.

- Propose plans for higher-risk studies. What are the levels of risk and nature of risk of various components? Justify the need for this research (i.e., describe the high pay-off) and present a rational scientific basis for your plan to achieve the goals. Although there is no specific requirement for preliminary data in this application, you must present a plausible flow to your reasoning. Use any combination of preliminary data (yours or others'), theory, mathematical reasoning, and clinical relevance to guide your thinking.

- Identify key scientific and technical hurdles, prioritized options for overcoming them, and alternative approaches. What will be the impact of failure to achieve certain of the goals?

- For the new studies under the NDC, describe dependencies (e.g., if certain data must be collected, or tools developed and applied, before subsequent studies can be done). Distinguish between short-term and long-term studies.

- Include a timeline of activities. This timeline should outline how the project's goals can be met within the time frame of a five year NDC award. The timeline will also assist the investigators and NIH in evaluating progress toward the project's goals. If appropriate, explicit, quantitative milestones should be presented.

Center and Network Organization

D. Resources

The ongoing research described above in section B is being done with other support. Document the resources available at the participating institutions and the enhanced capability of your center because of association with other centers or technical cores available to your NDC.

- How will the ongoing projects be enhanced by work at your NDC and vice versa?
- What resources are in place or need to be developed locally?
- How will you use nanotechnology and other resources that are available nationally?
- Do you have agreements in place for access to other facilities?

E. Center Structure

- Table of Key Personnel

  Include names, degrees, institutional affiliation, and expertise. Letters of collaboration must be included for all team members listed (see below; Section M. "Key Personnel and Consultant Letters"). Only key personnel should be included. Post-doctoral fellows, graduate students, technicians should not be included unless they are contributing to the intellectual development of your application or are essential for their particular expertise in completing proposed studies.

- Investigator interactions
- Core facilities (if appropriate)
- Management structure and plan.
- Scale-up plan

  As stated above, you only need to broadly state the expected use of additional funds in FY2008 and FY2009. If appropriate, refer to studies proposed in Section C, "New Studies and New Directions". For example, are additional funds needed for high throughput, generalization to other systems, anticipated new directions that depend on earlier work, etc.? In FY2007, detailed plans from awarded NDCs will be required.

NIH is not specifying a particular organizational structure for a NDC, as each applicant should develop the structure that would best promote the proposed research. However, note that the effectiveness of the proposed structure will be a criterion of the evaluation prior to an award, and its successful implementation will be monitored after an award is made.

The application should describe the specific administrative and organizational structure that will be used to support the research, and the synergies enabled by this structure. These plans will take into account that NDC projects will be multi-disciplinary and will draw on a variety of resources. For example, if core facilities or shared resources are required, describe their management and service to the research projects at your NDC. Explain how different components of the organization, including key personnel, will interact, why they are essential to accomplishing the goals of the research, and how the combined resources create capabilities that are more than the sum of the parts. Present evidence that the investigators can collaborate effectively. "Centers-without-walls" are welcome under this solicitation, but you must address how to overcome the potential difficulties created by being physically separated.

The P.I. or leadership team is responsible for developing and managing a decision-making structure and process for resource allocation, i.e. a management plan. This is particularly important, as NDCs are expected to pursue some high-risk/high-payoff strategies, and therefore must have in place the means to balance and re-balance funds and other resources. Although no specific percent effort is specified, a good management plan will require significant commitment of key personnel.

F. Network Structure

F1. Center Interactions. Describe how your NDC will interact with the other NDCs in the network. What administrative and scientific contributions will you make to the network, and what do you need from a network for your NDC to be successful? How do you envision the most effective interactions (e.g., balance of face-to-face versus telephone/video conferences)? On what schedule should network activities commence (e.g., what is the right balance of establishing "network" versus individual NDC activities)? Do you envision collaborative studies between your NDC and others within the network?

F2. Best Network (Optional). Three or four centers will be selected for awards and participation in the NDC network based on the synergies that we detect among the most meritorious centers identified. Your insight into the groups that might best complement your center will be considered as we make these determinations. The following requested information will inform the selection process but will not be used as review criteria for your NDC application. However, we consider your input a valuable part of the process as we develop the network.

You have heard presentations by all the CDA recipients and you have their abstracts. Briefly document synergies with other CDA teams where the goals, projects, and strengths might complement yours and would strengthen your attempt to achieve your vision of a Nanomedicine network. Although you may find synergies with several other groups, select the two or three other recipients that, along with your NDC, would provide the best national network of centers. You define what is "best" in terms of scientific goals, expertise, complementary approaches or model systems, etc. What other centers would be valuable additions to the program?

Assurances

G. Human Subjects and Animal Welfare

The time between receipt of your application (July 12, 2005) and awarding the centers in September 2005 is accelerated relative to standard NIH procedures. In addition, many specific experiments are not expected to be described in complete detail in your application so that required approvals by Institutional Review Boards (IRB) for studies with Human Subjects and/or by Institutional Animal Care and Use Committee (IACUC) regarding animal welfare cannot realistically be completed by the time of award. **No approvals are required at this time and completion of the Human Subjects and Vertebrate Animals sections are not required in your NDC application at this time.**

Unlike traditional 5-year grants, the extent of your studies and the scope of your project may be uncertain. If research activities involving human subjects or vertebrate animals are planned or may be planned at any time during the proposed project period, either at the applicant organization or at any other performance site or collaborating institution, then you should answer **"Yes"** for **"Humans Subjects"** and/or **"Vertebrate Animals"** on the application face page, even if you expect that the human subject research will be exempt from regulations for the protection of human subjects. However, if you already have studies planned that definitely will use human subjects or vertebrate animals, describe them in this portion of the application.

Before commencing work using human subjects or vertebrate animals, all assurances for safety and proper treatment and handling must be in place. **Awards will be issued with a restriction that requires approval of proposed protocols by:**

1) IRB for studies on human subjects and IACUC for vertebrate animal studies.

2) NIH staff.

After the award is made, you will need to submit a more detailed research plan when human subjects or vertebrate animals are used that must also include the required justifications and other information found on pages 32 to 34 of the PHS 398 instructions (http://grants.nih.gov/grants/funding/phs398/phs398.html)

H. Biohazards, Biotoxicity and Biocompatibility

There is growing awareness, in the scientific community and by the public, that nanoparticles and nanostructured surfaces may be highly reactive. This and other unique properties may bring great advances and capabilities but also may result in adverse effects on biological systems. This initiative bears the responsibility to investigate interactions between the materials and devices that are developed, and biological tissues, as well as promote responsible handling and disposal of the materials during the research. One of the goals of this initiative is to design particles, materials, and devices that can be used *in vivo*. Consequently, in the course of these studies, release of nanoparticles into the environment and/or use in the body could lead to unanticipated adverse

effects. As nanoparticles are synthesized or generated, biotoxicity[2] and biocompatibility[3] considerations must be addressed. The nanostructures and nanoparticles created by your research are potentially hazardous. Accordingly, the following are required:

1) You must include a plan that describes your approach to assessing the toxicity and biocompatibility of nanostructures created by your research. There are currently no specific NIH guidelines available so it is your responsibility to devise an effective plan to address these issues.[4]

2) You must submit a plan that describes your procedures for safely handling these potentially highly reactive particles that must be cosigned by your institutional safety officer.

3) Documentation must be submitted indicating that all lab personnel have completed an annual hazardous materials safety course.

Inadequate plans or documentation may require a restriction on awards until plans are approved by NIH.

Other Items

For information on the following, refer to p. 35 of the PHS 398 Instructions

I. Literature Cited

J. Consortium/Contractual Arrangements

K. Data and Resource Sharing

Several standard NIH sharing instructions are described below (p. 22) and this section of your application should address those that are relevant to items that your NDC will generate. In addition, for the network to operate effectively, data and or tools generated by projects currently in-progress need to be shared. Since this may raise questions regarding protection of intellectual property, you must also address the means by which you will reduce impediments to information sharing across the network. Acceptance of an award for an NDC indicates that your center will participate in the NDC network and is willing to share information, tools, and data, and technology in accord with NIH policies and additional network requirements.
A more comprehensive NIH policy requires that awardee recipients make unique research resources readily available for research purposes to qualified individuals within the scientific community after publication (NIH Grants Policy Statement http://grants.nih.gov/grants/policy/nihgps_2003/index.htm and http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_Part7.htm#_Toc54600131). Investigators

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[2] Toxicity refers to the dose of the material that causes the adverse health effect.
[3] Biocompatibility describes the condition under which the exposure does not disturb homeostasis or cause an adverse health effect.
[4] If NIH policies change and specific guidelines are issued, a revised plan may be required. Also, it is our expectation is that the NDC network eventually will address the elements required in an effective assessment plan. If so, plans may need to be modified in accord with these guidelines.

responding to this funding opportunity should include a plan for sharing research resources that addresses how unique research resources will be shared or explain why sharing is not possible.

The adequacy of the resources sharing plan and any related data sharing plans will be considered by Program staff of the funding organization when making recommendations about funding applications. The effectiveness of the resource sharing will be evaluated as part of the administrative review of each non-competing Progress Report (PHS 2590, http://grants.nih.gov/grants/funding/2590/2590.htm). See Section VI.3. Award Criteria.

L. Suggested Reviewers and Expertise

Technical experts will be recruited to participate in the review of the NDC applications. You may suggest reviewers who you think are appropriate to assess the merit of your application. Organize your list in outline form by areas of expertise. Include the investigator's name and institution. Your list will serve as a guide to assist us in assembling the panel. There are no guarantees that anyone listed will be recruited.

M. Key Personnel and Consultant Letters

Include letters from all individuals confirming their participation and describing their roles in the project. If any are paid consultants include rate/charge for consulting services.
Do not place these letters in the Appendix.

N. Appendix

Do not use the Appendix to circumvent the 35 page limitation of the research plan. An NDC application that does not observe these limitations will be returned

- Appendix material is to be submitted as a PDF file (refer to pages 8 and 16).
- Up to 10 manuscripts (*accepted* for publication), abstracts, patents, or other printed materials directly relevant to this project. *Do not include manuscripts* ***submitted*** *for publication.*
- Surveys, questionnaires, data collection instruments, clinical protocols, and informed consent documents.
- *Photographs, color images, and movies must be included in the Research Plan.*

O. Checklist (Refer to p. 36 of the PHS 398 Instructions)

Where to send your NDC applications and Appendix material:

****** NOTE *** Copies of your application must be sent to two different locations***
Do NOT send hard copies of Appendix material

1) Send the <u>original and 2 copies</u> to:

Center for Scientific Review
National Institutes of Health
6701 Rockledge Drive, Suite 1040
MSC 7710
Bethesda, MD 20892-7710 (US Postal Service Express or Regular mail)
or
Bethesda, MD 20817 (Express/Courier Non-USPS Service)
The telephone number is (301) 435-0715

Attach the RFA label or a facsimile, including the RFA number, to the bottom of the Face Page of the original application. The RFA label is under the general mailing label, following the Checklist and Personal Data pages.

2) Send <u>2 printed copies</u> and a <u>CD-ROM with your application and all Appendix material</u> saved as PDF files to:

Richard S. Fisher, PhD
NDC APPLICATION
National Eye Institute
Division of Extramural Research
5635 Fishers Lane MSC 9300
Bethesda, MD 20892-9300 (for FEDEX, etc., Rockville, MD 20852)
phone: 301-451-2020

Preparing your CD-ROM:

You must submit a copy of your NDC application and all appendix material on a PC compatible CD-ROM (using Windows XP). ***All items must be PDF files.*** Hard copies of Appendix material will not be accepted. An unpublished manuscript with embedded movies is considered a single item.

Please create 2 directories on the CD-ROM: Appendix Materials
NDC Application

PART III. Review Criteria

NDC applications will be evaluated in accord with the criteria listed below. Centers will be awarded based on these criteria and project team assessment of NDC integration in the network. The five main review criteria, **Significance, Approach, Innovation, Investigator, and Environment**, form the basis for evaluating peer-reviewed applications at the NIH. They are tailored here specifically for the NDC applications and are supplemented by additional criteria (given below).

The relative weight of the five criteria will not be specified and will be assigned as reviewers deem appropriate. However, **Innovation** and **Investigator** (i.e., the track record of the PI and leadership team for solving difficult technical and conceptual problems) will receive substantial attention in the review of these applications.

Significance: Does the application address an important biomedical problem? Does it encompass the elements of the NIH Nanomedicine vision? Does it generalize its vision, concepts, approaches and measurements to other model systems and diseases? If successful, will this center create something new that would not have been achieved without the Nanomedicine Initiative?

Approach: Are the conceptual or clinical framework, design, methods, and analyses adequately developed, well-integrated, well-reasoned, and appropriate to goals of the center, the network, and the NIH Nanomedicine initiative? Does the applicant acknowledge potential problem areas and consider alternatives? Is the applicant reaching beyond the safe, guaranteed work? Are new studies proposed that are more than simply an expansion of ongoing work? For the riskier, but potentially high-payoff components, are the scientific bases of the plan, and the elements of science and technology, where there may be knowledge gaps, clearly described? Are the performance criteria for declaring "success" adequately explained and justified? Is there a plan for evaluating progress and deciding when a project should be terminated or re-directed? Is there evidence of a multidisciplinary approach?

Innovation: Is the project original and innovative? For example: Does the project challenge existing paradigms or address an innovative hypotheses or critical barrier to progress in the field? Does the project develop or employ novel concepts, approaches or methodologies, tools, or technologies for this area? Does it propose to develop new measurement capabilities that enable important measurements that we either cannot make now, or can make only with difficulty?

Investigator: Are the investigators appropriately trained to carry out the work? Do the principal investigator and other key personnel have the experience to manage the NDC? Does the investigative team bring complementary and integrated expertise to the project? Do members of the leadership team have a track record of having solved difficult technological or conceptual problems? Have the necessary personnel been recruited for the proposed multidisciplinary studies? Is there evidence that the team, or a subset of the team, has worked together productively in the past? Are there adequate plans to achieve smooth and efficient collaboration, and to share and allocate resources effectively?

Environment: Does the scientific environment contribute to the probability of success? Do the proposed studies benefit from unique features of the scientific environment, or subject populations, or employ useful collaborative arrangements? Is there evidence of institutional

support? Is there a plan to integrate effectively other (institutional, regional, national, international) resources that augment those available directly to the participating investigators? Has the team contacted other centers or institutions to take advantage of the burgeoning work and tools in nanotechnology?

Additional Criteria:

- Is the effort proposed for the NDC clearly delineated from the effort of ongoing, funded (or pending funding) research?
- Will the center identify new, quantitative knowledge of the biological systems?
- Has the applicant enumerated the specific knowledge gaps that would be filled?
- Is there a description of the new quantitative measurement capabilities that would be developed?
- Is there a plan for developing new, or enhancing current, mathematical models?
- Does the applicant relate the approaches and the novel measurements to specific gaps in knowledge of biological design or to key parameters of the mathematical models being developed?
- Is there a discussion of potential engineering principles associated with, or that could be applied to, Nanomedicine?
- Does the applicant justify how data quality and measurement uncertainties would be addressed and how that would affect quantitative modeling?
- Does the applicant propose to make novel measurements in living cells?
- Does the applicant describe the medical relevance or eventual application to medical needs? Is there evidence that the project is driven by curing disease and/or repairing tissue?
- Is there a plan for scaling up operations? Does the plan present alternatives since there is a likelihood that some studies may fail?

PART IV. Award Management and Administrative Information

Flexible Research Authority (FRA). Centers will be awarded initially for up to five years and the Notice of Award will state that "Flexible Research Authority" will apply for the duration of the award (up to 5 years). Consistent with these authorities, the management activities and structure may change as the research needs of the individual centers and the National NDC Network evolve.

Terms and Conditions of Award. Awards issued under FRA are subject to the terms and conditions detailed in this RFA and any subsequent updates (see above; p. 4). Absent a specific mention of terms in this document and updates, the terms and conditions in the current NIH Grants Policy Statement (rev. 12/2003, http://grants.nih.gov/grants/policy/nihgps_2003/index.htm) apply to these awards. Acceptance that award management will remain flexible to accommodate the needs of the initiative and NDC network will be specified as a condition of the award.

Center and Network Management. As outlined in this document, especially given the wide latitude of FRA, the network of centers will work closely with NIH staff and a Scientific Advisory Panel in those aspects of scientific and technical management of the project as described below.

For the NDC network, a Steering Committee will consist of the principal investigator (or designated alternate) from each of the centers, and staff from NIH. Each center will be required to participate in all official steering committee meetings. An Advisory Panel will consist of individuals (up to 8) with appropriate scientific knowledge and experience, who are not NIH extramural program staff or associated directly with any of the NDCs, who will be selected by the NIH program staff. The Advisory Panel will provide scientific, technical, and budgetary advice to the NIH. The NIH staff will call separate meetings of the Steering Committee and the Advisory Panel at least annually; one or more NIH officials will be present at each of these meetings. Meetings will be held either at NDCs or the NIH, and estimated travel expenses should be included in the proposed NDC budget. No supplementary funds are expected to be available for meeting travel.

Meetings of the network steering and advisory committees will be primarily scientific in nature, to share information about progress, identify and facilitate potential collaborations, and share information about emerging concepts and resources. The meetings will also be a focal point for monitoring progress, exploring new scientific opportunities, and evaluating the current and future investment of initiative funds. The meetings will facilitate the collaborative nature of a network of centers. Meetings for wider participation of more of the research staff of each of the NDCs, and other interested parties, will be coordinated with the steering and advisory committee meetings.

Since Nanomedicine is an emerging field, the directions and needs of the field will develop with time. Examples of such needs that the network will address include, but are not limited to topics described above, e.g., human and animal subjects; laboratory safety and materials disposal; ethical, legal and societal dimensions[5]; and resources development and sharing.

[5] The NIH is examining the ethical, legal and societal dimensions of the intersection of nanotechnology with biomedicine. Nanomedicine Development Center personnel will be expected to participate substantively as discussions progress. Depending on the outcome of this process, the Nanomedicine Development Centers may also play a role in the ensuing research and related activities.

Reports. NDC principal investigators may be required to produce more detailed annual progress reports than are typically required for an NIH grant. NIH staff may require other reports periodically as a consequence of meetings of the Network committees, or other NIH requirements (e.g., related to FRA, etc.). Formats for these reports will be provided, and may change as the needs of the program evolve. NIH staff and the Advisory Panel members will receive these reports and may elect to share some or all of any report with the other NDCs within the network.

NIH Oversight. There will be significant involvement of NIH staff and external advisors throughout the project period. Oversight involves examining whether adequate progress is being made using valid reasoning and approaches. Traditional NIH oversight involves program and grants management staff of the funding institute. Because Nanomedicine is multidisciplinary and the science is relevant to the missions of most or all the NIH institutes, oversight will involve a team of program staff that will likely include several members of the project team but may include program staff from other NIH institutes. The NIH program oversight committee will determine, in consultation with the NDCs and the network advisory committees, whether progress is satisfactory and whether resources should be redirected.

Resource Allocation. Under Flexible Research Authority, NIH has the responsibility to monitor progress under the NDC awards. Because more risk will be accepted in the development of the NDC research plans, there may be a need to terminate all or part of a particular avenue of research. The goal, of course, is to balance risks with benefits and make adjustments during a project so that termination of awards is unnecessary. NIH will work with the Steering Committee and Advisory Panel in assessing progress and developing alternatives to modify research plans when there is evidence that progress is insufficient.

There was recognition at the CDP meeting that centers will achieve variable levels of success at different rates. There was an understanding that relatively risky projects may fail for many different reasons, but may also bring revolutionary advances. Failure may be recognized quickly, but it is also possible that studies may appear promising at first, but the project may eventually fail after several years. The association of centers in a network provides an opportunity for wider influence on center activity. Oversight committees and NIH staff will play an important role in monitoring progress at individual centers while still encouraging independence and creativity. There are several possibilities that might require intervention and re-allocation of resources. For example:

- A project might require resources that were not anticipated either to break through an obstacle to success or, alternatively, because the project is a great success.
- Individual projects may be failing with little or no hope of success. This could be for a variety of reasons. For example, maybe a project is not clearly articulated because the technical path is not obvious. Each center will have its own process for evaluating progress on projects, regardless of the risk level, and should make decisions about when to discontinue projects that are not working. Centers will report on such decisions, which will also be discussed by the network advisors.

- Even though a project appears promising, it may be determined that progress is too slow (e.g., there may be other technologies required to advance the work), and therefore, the limited resources of this program will have to be used in other ways.
- A project may be making good progress, but may be conventional and therefore eligible for funding by standard grant mechanisms outside this program.

The network will strive to achieve a balance between funds that each center can rely upon to maintain its core activities and funds that are set aside to meet emerging needs. Procedures will be developed to allocate the set aside funds, using evaluation criteria appropriate for the particular purpose.

Model for Resource Allocation

Allocation and management of funds will remain flexible throughout the project. The following description represents current thinking about a framework for initial funds allocation. The model assumes that 3 NDCs will be funded in 2005 and 3 more in 2006. **However, this is only an example and actual funding levels will be determined after applications are reviewed in response to this RFA and the re-issue in FY2006.** The model assumes that 15% of the program's funds will be set aside for distribution in response to needs and opportunities. **Although the outline here is specific, it is subject to change and may evolve based on the needs of the individual centers and network.** This flexibility, in accord with FRA (see above), will be explicitly stated as a term of the award. (Dollar amounts, in millions, are total costs and are approximate).

In FY2005, $6M will be divided among three centers ($1.7M per center + $0.9M set aside).

Fiscal Year	Total Nanomedicine Program $ (million)	Total # of Awarded Centers	NDC base $ (million per NDC)	Network Set Aside $* (million)
2005	6	3	1.7	0.9 **
2006	12	6	1.7	1.8
2007	12	6	1.7	1.8
2008	25	6	1.7 ***	3.8
2009	25	6	1.7 ***	3.8

* A process will be developed to apply for, and evaluate proposals to use set aside funds at least once each year. Set aside funds (15% of total available to the initiative) will be awarded for a maximum term of one year and will not be considered part of the center's base award. More frequent evaluation may be required as the program develops.

** In practice, set aside funds will be awarded along with the base funds to each of the host institutions of the NDCs. Award notices will include a restriction of the set aside funds where NIH approval is required before spending. If funds are re-allocated to a different center, the

Notice of Awards to all the centers affected by the reallocation of funds will be revised. For example, in FY2005, centers will be awarded on or about September 30, 2005. If those funds are to be re-allocated to a different center in FY2006, then the Notices of Awards will be adjusted to reflect the change. The following example demonstrates this implementation:

For NDC #1: FY2005 base amount = $1.7 M
Set aside (restricted) = 0.3 M
NDC #1 Award amount (FY2005) = 2.0 M

FY2006 base amount = 1.7 M
Set aside (restricted) = 0.3 M
NDC #1 Award amount (FY2006) = 2.0 M

Assume a decision is made to re-allocate set-aside funds in both fiscal years from NDC #1 to NDC #2:

NDC #1 revised award amount (FY2006) = $1.4 M

The decrease of the amount awarded to NDC #1 ($0.6 M) would be matched by an equal increase of the amount awarded to NDC #2

*** In FY2008 and 2009, an additional $11.0 million will be available for scale-up of centers on a competitive basis. A process to apply for those funds and evaluate those requests will be established in FY2007.

PART V. REQUIRED FEDERAL CITATIONS

Use of Animals in Research:
Recipients of PHS support for activated involving live, vertebrate animals must comply with PHS Policy on Humane Care and Use of Laboratory Animals (http://grants.nih.gov/grants/olaw/references/PHSPolicyLabAnimals.pdf) as mandated by the Health Research Extension Act of 1985 (http://grants.nih.gov/grants/olaw/references/hrea1985.htm), and the USDA Animal Welfare Regulations (http://www.nal.usda.gov/awic/legislat/usdaleg1.htm) as applicable.

Human Subjects Protection:
Federal regulations (45CFR46) require that applications and proposals involving human subjects must be evaluated with reference to the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained (http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm).

Data and Safety Monitoring Plan:
Data and safety monitoring is required for all types of clinical trials, including physiologic toxicity and dose-finding studies (phase I); efficacy studies (Phase II); efficacy, effectiveness and comparative trials (Phase III). Monitoring should be commensurate with risk. The establishment of data and safety monitoring boards (DSMBs) is required for multi-site clinical trials involving interventions that entail potential risks to the participants (NIH Policy for Data and Safety Monitoring, NIH Guide for Grants and Contracts, http://grants.nih.gov/grants/guide/notice-files/not98-084.html).

Sharing Research Data:
Investigators submitting an NIH application seeking $500,000 or more in direct costs in any single year are expected to include a plan for data sharing or state why this is not possible (http://grants.nih.gov/grants/policy/data_sharing).

Investigators should seek guidance from their institutions, on issues related to institutional policies and local IRB rules, as well as local, State and Federal laws and regulations, including the Privacy Rule. Reviewers will consider the data sharing plan but will not factor the plan into the determination of the scientific merit or the priority score.

Sharing of Model Organisms:
NIH is committed to support efforts that encourage sharing of important research resources including the sharing of model organisms for biomedical research (see http://grants.nih.gov/grants/policy/model_organism/index.htm). At the same time the NIH recognizes the rights of grantees and contractors to elect and retain title to subject inventions developed with Federal funding pursuant to the Bayh Dole Act (see the NIH Grants Policy Statement http://grants.nih.gov/grants/policy/nihgps_2003/index.htm). All investigators submitting an NIH application or contract proposal, beginning with the October 1, 2004, receipt date, are expected to include in the application/proposal a description of a specific plan for sharing and distributing unique model organism research resources generated using NIH funding or state why such sharing is restricted or not possible. This will permit other researchers to benefit from the resources developed with public funding. The inclusion of a model organism sharing plan is

not subject to a cost threshold in any year and is expected to be included in all applications where the development of model organisms is anticipated.

Inclusion of Women And Minorities in Clinical Research:
It is the policy of the NIH that women and members of minority groups and their sub-populations must be included in all NIH-supported clinical research projects unless a clear and compelling justification is provided indicating that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43). All investigators proposing clinical research should read the "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research" (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html); a complete copy of the updated Guidelines is available at http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm. The amended policy incorporates: the use of an NIH definition of clinical research; updated racial and ethnic categories in compliance with the new OMB standards, clarification of language governing NIH-defined Phase III clinical trials consistent with the new PHS Form 398, and updated roles and responsibilities of NIH staff and the extramural community. The policy continues to require for all NIH-defined Phase III clinical trials that: a) all applications or proposals and/or protocols must provide a description of plans to conduct analyses, as appropriate, to address differences by sex/gender and/or racial/ethnic groups, including subgroups if applicable; and b) investigators must report annual accrual and progress in conducting analyses, as appropriate, by sex/gender and/or racial/ethnic group differences.

Inclusion of Children as Participants in Clinical Research:
The NIH maintains a policy that children (i.e., individuals under the age of 21) must be included in all clinical research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them.

All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines" on the inclusion of children as participants in research involving human subjects (http://grants.nih.gov/grants/funding/children/children.htm).

Required Education on the Protection of Human Subject Participants:
NIH policy requires education on the protection of human subject participants for all investigators submitting NIH applications for research involving human subjects and individuals designated as key personnel. The policy is available at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html.

Human Embryonic Stem Cells (hESC):
Criteria for federal funding of research on hESCs can be found at http://stemcells.nih.gov/index.asp and at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-005.html. Only research using hESC lines that are registered in the NIH Human Embryonic Stem Cell Registry will be eligible for Federal funding (http://escr.nih.gov). It is the responsibility of the applicant to provide in the project description and elsewhere in the application as appropriate, the official NIH identifier(s) for the hESC line(s) to be used in the proposed research. Applications that do not provide this information will be returned without review.

Public Access to Research Data through the Freedom of Information Act:
The Office of Management and Budget (OMB) Circular A-110 has been revised to provide public access to research data through the Freedom of Information Act (FOIA) under some circumstances. Data that are

(1) first produced in a project that is supported in whole or in part with Federal funds and (2) cited publicly and officially by a Federal agency in support of an action that has the force and effect of law (i.e., a regulation) may be accessed through FOIA. It is important for applicants to understand the basic scope of this amendment. NIH has provided guidance at http://grants.nih.gov/grants/policy/a110/a110_guidance_dec1999.htm. Applicants may wish to place data collected under this RFA in a public archive, which can provide protections for the data and manage the distribution for an indefinite period of time. If so, the application should include a description of the archiving plan in the study design and include information about this in the budget justification section of the application. In addition, applicants should think about how to structure informed consent statements and other human subjects procedures given the potential for wider use of data collected under this award.

Standards for Privacy of Individually Identifiable Health Information:
The Department of Health and Human Services (DHHS) issued final modification to the "Standards for Privacy of Individually Identifiable Health Information," the "Privacy Rule," on August 14, 2002. The Privacy Rule is a federal regulation under the Health Insurance Portability and Accountability Act (HIPAA) of 1996 that governs the protection of individually identifiable health information, and is administered and enforced by the DHHS Office for Civil Rights (OCR).

Decisions about applicability and implementation of the Privacy Rule reside with the researcher and his/her institution. The OCR website (http://www.hhs.gov/ocr/) provides information on the Privacy Rule, including a complete Regulation Text and a set of decision tools on "Am I a covered entity?" Information on the impact of the HIPAA Privacy Rule on NIH processes involving the review, funding, and progress monitoring of grants, cooperative agreements, and research contracts can be found at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-025.html.

URLs in NIH Grant Applications or Appendices:
All applications and proposals for NIH funding must be self-contained within specified page limitations. Unless otherwise specified in an NIH solicitation, Internet addresses (URLs) should not be used to provide information necessary to the review because reviewers are under no obligation to view the Internet sites. Furthermore, we caution reviewers that their anonymity may be compromised when they directly access an Internet site.

Healthy People 2010:
The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS-led national activity for setting priority areas. This RFA is related to one or more of the priority areas. Potential applicants may obtain a copy of "Healthy People 2010" at http://www.health.gov/healthypeople.

Authority and Regulations:
This program is described in the Catalog of Federal Domestic Assistance at http://www.cfda.gov/ and is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review. Awards are made under the authorization of Sections 301 and 405

of the Public Health Service Act as amended and Section 217 (a) and (b) of the FY 2005 Consolidated Appropriations Resolution P.L. 108-07. All awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement. The NIH Grants Policy Statement can be found at http://grants.nih.gov/grants/policy/policy.htm.

PART VI. Terms and Conditions

This award provides support for Nanomedicine Development Centers (NDC) that participate in the NIH Nanomedicine Development Center Network (NNDCN). THIS AWARD IS FUNDED BY THE NATIONAL INSTITUTES OF HEALTH THROUGH THE NIH ROADMAP FOR MEDICAL RESEARCH. Any publications or other acknowledgements should indicate that "This work was funded by the National Institutes of Health through the NIH Roadmap for Medical Research". Information on the Nanomedicine Roadmap can be obtained from http://nihroadmap.nih.gov/nanomedicine. Support for the NIH Roadmap initiatives is provided by all Institutes and Centers. The National Eye Institute (NEI) is the administrative institute for the Nanomedicine Initiative.

Notice of Award and FRA. The NIH policy for research supported under this award is governed by Flexible Research Authority contained in the **P.L. 108-447, CONSOLIDATED APPROPRIATIONS ACT FOR FY 2005:**

> **SEC. 217. (a) AUTHORITY**.--Notwithstanding any other provision of law, the Director of the National Institutes of Health may use funds available under section 402(i) of the Public Health Service Act (42 U.S.C. 282(i)) to enter into transactions (other than contracts, cooperative agreements, or grants) to carry out research in support of the NIH Roadmap Initiative of the Director.
>
> **(b) PEER REVIEW**.--In entering into transactions under subsection (a), the Director of the
> National Institutes of Health may utilize such peer review procedures (including consultation
> with appropriate scientific experts) as the Director determines to be appropriate to obtain assessments of scientific and technical merit. Such procedures shall apply to such transactions in lieu of the peer review and advisory council review procedures that would otherwise be required under sections 301(a)(3), 405(b)(1)(B), 405(b)(2), 406(a)(3)(A), 492, and 494 of the Public Health Service Act (42 U.S.C. 241, 284(b)(1)(B), 284(b)(2), 284a(a)(3)(A), 289a, and 289c).

In accord with the authority specified above in Section 217 (a), awards to support the NDCs will not be considered contracts, cooperative agreements or grants. However, funds will be disbursed using a standard NIH Notice of Grant Award. The administrative and funding instrument used for this Nanomedicine program will be the PN2 mechanism. This is a new mechanism developed specifically for this new type of transaction to fund Nanomedicine Development Centers using FRA. PN2 Nanomedicine Development Centers will operate within the NIH Nanomedicine Development Center Network (NNDCN also referred to as "the network"). The awards will be issued in response to NOT-RM-05-010, released on April 13, 2005 in the NIH Guide to Grants and Contracts, and is subject to the conditions specified in Parts I, II, III, IV, V, and VI of this RFA (contained herein).. Consistent with this RFA, the primary responsibility for the activity resides with the awardee(s) for the project as a whole, although specific tasks and activities in carrying out the studies will be shared among the awardees and the NIH Nanomedicine Project Team, and other groups (as defined in this RFA).

Under the PN2 award mechanism, the NIH purpose is to support and stimulate the recipients' activities by involvement in and otherwise working jointly with the award recipients in a partnership role; it is not to assume direction, prime responsibility, or a dominant role in the activities. Project management will include reallocation of funds as specified in PART IV.

NIH Staff Responsibilities. NIH oversight will be governed by the NIH Nanomedicine Initiative Project Team (NIPT) which will have substantial scientific-programmatic involvement. However, the role of the NIPT will be to facilitate and coordinate but not direct activities. The NIPT will consist of representatives of at least 8 NIH institutes and centers and will be chaired by a Project Team Leader. The Project Team Leader will be the point-of-contact for the principal investigators of each NDC. The NIPT will:

- Assist in avoiding duplication of effort across awardee projects
- Help coordinate collaborative research efforts that involve multiple awardees within the NNDC network
- Review and approve critical stages in the research program before subsequent stages are implemented
- Assist in the interaction between the awardee and investigators at other institutions
- Be a voting member of the Steering Committee and its subcommittees (one vote)
- Help the Steering Committee develop and draft operating policies and policies addressing recurring situations that require coordinated action where necessary
- Review the scientific progress of the individual awards for compliance with operating policies developed by the Steering Committee, and may recommend to the NIH to withhold support, suspend, or terminate an award for lack of scientific progress or failure to adhere to the terms of the award and/or the policies established by the Steering Committee.
- Determine resource needs and directing the re-allocation of set-aside funds.
- Determine a review process and decision process for scale-up funds in FY2008 and FY2009.
- Recommend, in consultation with the Scientific Advisory Panel (see below), additional research endeavors within the constraints of the approved research and negotiated budget and the scope of this RFA.
- Advise on the integration of additional centers into the NNDCN in FY2006.
- May consult with other NIH staff as well as non-NIH experts in the field in order to carry out these responsibilities.
- Be responsible for any other programmatic activities typically undertaken by NIH program if not otherwise specified above.

In addition, the NEI will designate a Grants Management Specialist to provide fiscal and administrative oversight of this award.

Principal Investigator Rights and Responsibilities. The PI will coordinate project activities scientifically and administratively at the awardee institution, including research design and protocol development, data collection, quality control, data and safety monitoring plan for any studies involving human subjects, final data analysis and interpretation, and preparation of publications.

The PI will have the primary responsibility for defining the details for the projects within the guidelines of this RFA and for performing all scientific activities. The PI will be responsible for collaborations between his/her NDC and the NNDCN. The PI will agree to accept close coordination, cooperation, and participation of NIH staff in those aspects of scientific and technical management of the project as described below. Specifically, the PI will:

- Determine experimental approaches, design protocols, set project milestones, and conduct experiments
- Propose protocol modifications as required
- Analyze and interpret research data
- Release data according to the approved plans for timely sharing of research resources and data generated through the award, and publish results, as agreed upon by the Steering Committee
- Establish an Internal Advisory Committee to provide scientific and administrative oversight. The Internal Advisory Committee will be composed of the lead institute personnel, external scientific advisors and other technical or research personnel. The committee is expected to meet at least twice a year. Minutes of these meetings will be made available to the NIPT upon request and will be available to the network Advisory Panel (see p. 19)
- Serve on the Steering Committee
- Provide information to the NIPT concerning progress by submitting periodic progress reports in a standard format, as agreed upon by the Steering Committee and Scientific Advisory Panel
- Accept and implement all scientific, practical, and policy decisions, common guidelines and procedures approved by the Steering Committee and Scientific Advisory Panel
- Share facilities, research resources, tools, and data of interest to those facilities with other awardees, as directed by the Steering and Advisory Committees; share standardized information on new developments and/or methods for solving obstacles with the investigators funded through this initiative and with the NIPT
- Prepare for annual site visits by NIPT for programmatic and/or administrative purposes.

Awardees will retain custody of and have primary rights to the data, software, and tools developed under these awards subject to Government rights of access consistent with current DHHS, PHS, and NIH policies.

Collaborative Responsibilities.

Steering Committee (refer to p.19, "Center and Network Management"). The NIPT and PIs of the NDCs under this RFA will be responsible for forming a Steering Committee as defined on p. 19. The Steering Committee will act as the main governing board that will review the progress of the research activities, develop collaborative protocols, identify technological impediments to the progress, select strategies to surmount them, and identify opportunities for sharing techniques and tools developed within each individual project and each center within the network. The Steering Committee will:

- Optimize the flow of information and communication within the network.

- Play a key role in standardizing data collection, reporting, and generalizing across the network.
- Be instrumental in disseminating research results within the network and into the public domain.
- Monitor developments of external programs at external nanotechnology and Nanomedicine centers as they may relate to the NIH NDCs.
- Advise the NIPT of scientific developments and opportunities that may enhance the goals of the program.
- Help to develop uniform procedures and policies, for the governance of the awards under this RFA.
- Provide input and recommendations to NIPT with respect to allocation of set-aside, re-allocation and/or redistribution of resources as implemented under FRA.
- Monitor, develop, and implement quality control procedures that assure consistency across Centers.
- Serve as a venue for coordination on improving the state of the art, for example by reporting progress, disseminating best practices and collectively evaluating new procedures, resources, and technologies.
- Be responsible for coordinating NDC efforts within the network and is the primary means of interaction with the NIPT. Schedule meetings and conference calls as necessary.
- Determine frequency and need for meetings with wider participation of more of the research staff from each NDC. Monitor all aspects of arrangements and content of these meetings.
- Provide information and guidance to NDC personnel with respect to NIPT award management and use of FRA in implementing the goals of the NIH Nanomedicine initiative
- Develop a plan for terminating projects that become unpromising or unproductive.

The Steering committee will be composed of the PI from each NDC and one or more members of the NIPT. The PI from each project will have one vote and the NIPT will have one vote. The Steering Committee may, as it deems necessary, invite additional, non-voting scientific advisors to meetings at which research priorities and opportunities are discussed.

There will be two meetings of the Steering Committee in the first two years and at least one meeting per year in the following years. The first meeting of the PIs funded under this RFA will be a Planning Meeting in the Bethesda, MD area soon after awards are issued. At the first Steering Committee meeting the members may: (a) draft a charter to detail policies and procedures and develop a process for monitoring compliance with the policies and procedures and for recommending that the NIPT act on evidence of non-compliance with Steering Committee policies; (b) agree upon the terms of the charter; (c) discuss the approaches that were proposed in the project applications and any relevant new information, and set initial priorities for the projects to be pursued; and (d) develop procedures and policy for determining progress and support for projects – especially high risk projects – that may take longer to come to fruition but are important to further the goals of the program.

Scientific Advisory Panel (refer to p. 19)

The Scientific Advisory Panel (SAP) will be responsible for reviewing and evaluating the progress of the awardees toward meeting their individual and collective goals. The SAP will provide

recommendations to the NIPT about continued support of the individual projects and the group of projects awarded under this RFA. The Advisory Panel will be composed of up to 8 senior scientists with relevant expertise (see p. 19). The membership of the Scientific Advisory Panel may be enlarged permanently, or on an ad hoc basis, as needed. The Scientific Advisory Panel will meet at least once a year. During part of this meeting, there will be a joint meeting with the Steering Committee to allow the Scientific Advisory Panel members to interact directly with the awardees. Annually, the Scientific Advisory Panel will make recommendations regarding progress of the individual and collective group of projects and centers and present advice about changes, if any, to the NIPT.

Resource Allocation

Flexibility in award management is considered an integral part of the use of FRA. A process will be established to evaluate NDC proposals for using set aside funds (refer to Part IV, Model for Resource Allocation, p.21). At least once each year, NDC proposals will be presented to the Steering Committee by each of the NDC PIs. The Steering committee will provide recommendations to the NIPT for allocating funds. The NIPT will determine resource allocation with additional input from the Scientific Advisory Panel if required. The proposal format and requirements will be developed and may change as the program progresses. Similarly, proposals for scale-up funds that are available in FY2008 and FY2009 will be presented to the Steering Committee, which, in turn, will provide recommendations to the NIPT. NIH staff will not vote on any steering committee recommendations to NIPT.

Dissemination of Research Results

This initiative encourages investigators to facilitate translating effective interventions and tools into practice. As part of the NIH commitment to the rapid translation of research evidence into practice, applicants should include explicit plans to disseminate research results into practice.

Guidance for Preparation of an Intellectual Property Management Plan.

Intellectual property management plans are required; it is not necessary to include the final plan approved by all parties in the NDC application, but final, approved plans will be expected on or before August 26, 2005 before the NDC applications are reviewed on August 31-September 2, 2005. The NIPT will consider the adequacy of the plans in determining whether to recommend an application for award. The approved plans would become a condition of the award and Progress Reports must contain information on activities for the sharing of research resources and intellectual property.

In the development of any research resource sharing and intellectual property management plans, applicants should confer with their institutions' office(s) responsible for handling technology transfer related matters and/or sponsored research. If applicants or their representatives require additional guidance in preparing such plans, they are encouraged to make further inquiries to the appropriate contacts listed above for such matters.

The intellectual property management plans expected under this RFA should address the following components:

1. Invention Disclosure and Patent Management

The Bayh-Dole Act and subsequent amendments addressing "Rights to Inventions Made by Nonprofit Organizations and Small Business Firms", as codified in 37 CFR 401, confers rights and responsibilities for inventions arising from federally funded grants. As part of the Intellectual Property (IP) Management Plan, applicants should define procedures for documenting and patenting new inventions arising from the work funded by this RFA. These should include:

- Record Keeping- To document discoveries made in the course of device development, applicants should describe institution policies for maintaining proper records.
- Invention Disclosure- The IP Management Plan should identify the institutional mechanism for reporting inventions, specifying the responsible office and forms. This plan should include provisions to establish appropriate invention disclosures prior to publication or presentation of project data, novel biomarker identification, or prototype design and Confidentiality Agreements amongst collaborators.
- Patenting - The IP management plan should include the institutional process and timetable for deciding whether to retain title on inventions, filing U.S. and foreign patent applications, and notifying NEI. Recipients of federal funds must disclose each new invention to the funding agency within two months after disclosure in writing to the institution. Describe institutional policies for patent searches and basis for filing provisional patents.
- Patent Reporting- Summarize the institutional mechanism for providing patent and licensing information to the appropriate government agency, including:

  • Office of Policy for Extramural Research Administration (OPERA) notification of any invention developed under funding for this project and provision of a non-exclusive, nontransferable, irrevocable, paid-up license.
  • Annual Invention Utilization Report documenting the status of licensing and development, including date of first commercial sale or use and gross royalties received. Reporting requirements can be satisfied by electronic data entry into the Interagency Edison system.
  • Final Invention Statement (form HHS 568) should be sent to NEI prior to grant closeout.

2. Licensing and Commercialization

The IP management plan should identify the institutional office responsible for technology licensing and outline potential strategies for licensing the prototype device for commercialization. Provisions for dissemination and licensing may include:

- Material Transfer Agreement- To encourage further research and development by not-for-profit institutions, awardees should disseminate information and reagents developed in this grant consistent with the NIH Research Tools Policy (http://ott.od.nih.gov/RTguide_final.html), such as through the Simple Letter Agreement (SLA).
- Option- A limited time option may be granted to an existing or potential partner during the period of development, leading to negotiation of a subsequent license for commercial purposes to the extent consistent with NIH policies, e.g., see http://iedison.gov/Edison/sponsored.html.

- Non-exclusive License
- Exclusive License
- Company spin-outs
- Other novel commercialization strategies

3. Inter-Institutional Agreement

If investigators in the grant application are collaborators from multiple independent institutions, the IP Management Plan should include an inter-institutional agreement for coordinating patent prosecution, licensing, and for sharing royalties amongst institutions and investigators. This agreement should specify the lead office for patenting and licensing inventions that arise from the collaboration. A uniform policy on record keeping and reporting should also be presented.

This guidance is provided **to assist** applicants in preparing the intellectual property management plans to encourage partnerships with industry in order to meet certain programmatic objectives and goals of particular funding announcements. Applicants are encouraged to use their own discretion to independently develop and submit their own plans for consideration.

Terms and Conditions of the PN2 Award under FRA

The NIH Grants Policy Statement (rev, 12/2003) is that standard terms and conditions for the FRA PN2 awards. Exceptions to the NIHGPS will be noted in the NDC RFA Instructions and the Award Notice.

Non-competing continuation applications should be submitted using the PHS 2590 <http://grants.nih.gov/grants/funding/2590/2590.htm> (rev. 9/2004). Recipients are to prepare a complete PHS 2590, including a detailed budget. Additional details on the requirements for the progress report will be distributed to the PN2 award recipients after the awards have been issued.

Carryover of Unobligated Balances

Use of unobligated balances is restricted and carryover of unobligated balances from one budget period to the next always requires NIH awarding office prior approval

Program Income

Program income earned during the period of support is subject to the deductive alternative.

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Email Questions and Responses

The following questions and responses were sent directly to the PIs and other designated individuals on applicant teams between May 10, 2005 and the release of this part of the RFA (Part VI).

Response #1:

As I mentioned, the RFA instructions supercede the PHS 398 instructions when there is a conflict.

We will be strict with respect to font type and size in the research plan. However, NIH biosketches do not have to be revised (as long as they are accurate). Also, you should certainly use a symbol font for Greek letters where necessary. Finally, the PHS 398 instructions indicate that "a smaller font size may be used for figures, graphs, diagrams, charts, tables, figure legends, and footnotes, but this type must follow the font typeface requirement and be readily legible".

This is fine, just keep in mind that clear, easily legible type is to your advantage in all parts of the application, and be sure that you are not using smaller text to circumvent the page limitations.

Question #2:

I have a question regarding the budget. Does it remain relatively flat over 5 years (1.7M in your example) or we can scale it up in years 4 and 5 when the funding is increased (please see example on p. 21 of the RFA)?

Response #2:

Although the example shown on p.21 indicates a sample budget of 1.7M per year, the table footnote mentions the scale-up funds that will be available in the final 2 years. Your budget should reflect your requirements based on the work proposed for all years. However, as mentioned on p.7:

You may submit plans for scale-up in FY2008 and FY2009, but no firm commitments will be made by NIH in the original award. A detailed request will be required in FY2007 that will be subject to additional review by NIH staff and possibly an outside review panel.

Given that you are proposing bold, new studies. We understand that the progress and the science will guide your directions in future years. For this reason, updated budgets will be requested in FY2007 that will reflect your requirements and will include available scale-up funds. The extent to which you address this increase of funds in your application is left to your discretion.

Question #3:

We are working on the budget for the Nanomedicine Center application. Will the funding mechanism be that of a grant such as R01 or P01, or will it be a “cooperative agreement”?

Response:

In accord with Flexible Research Authority (FRA), the Nanomedicine Development Centers will be funded by new mechanisms tailored to the needs of a network of awardees**.** This will provide needed flexibility, depending on the nature of different project goals, team structures, and participation by various sectors (e.g., academia, government labs, industry). In other words, the

mechanism for awarding the NDCs may have elements of several other mechanisms and may have additional constraints and/or flexibility when compared to existing mechanisms.

Question #4:
I understand that we should submit a detailed budget for $1.7 million per year for five years, plus we are invited to describe ways we could use more money;i.e., the 15% set-aside in each year, and possible expansion of the base budget after the first two years. Do I have that right?

RESPONSE:

This is correct. However, be aware that the needs for the set-aside money will be examined at least once per year. We expect these needs to change, and the funds may be targeted to meet unanticipated opportunities and/or challenges. Consequently, your plans for set-aside money may be more useful in the first year, but thereafter, might change dramatically. We expect this and will certainly not hold you to these estimates. The issue of scale-up was mentioned specifically in the RFA:

> You may submit plans for scale-up in FY2008 and FY2009, but no firm commitments will be made by NIH in the original award. A detailed request will be required in FY2007 that will be subject to additional review by NIH staff and possibly an outside review panel.

QUESTION #5:

Can the appendix include PDF's of previously *published* papers? Or should it only include manuscripts that are *accepted but unpublished*?
(It is clear that *submitted* manuscripts should NOT be included).

RESPONSE:

We stated that the appendix should not include published papers, only accepted but unpublished manuscripts.

OPTIONAL: However, since the applications will be submitted on CD-ROMs, as a convenience to reviewers, if you wish, you may include a separate folder on the CD-ROM containing published papers.

Label the folder: "Published Papers"
Each paper should be: a separate PDF file Format of Filenames: last name of first author-year, that is: Fisher-2005. If there is more than one, add a, b, c... after the year.

Remember, you are NOT required to do this.

QUESTION #6:

M. Key Personnel and Consultant Letters Include letters from all individuals confirming their participation and describing their roles in the project. If any are paid consultants include rate/charge for consulting services. Do not place these letters in the Appendix.

Do you need letters even from key personnel who are at the home institution?

RESPONSE:

In a standard application, a collaborator who is listed as key personnel does not have to have a letter. They provide a biosketch instead. The biosketch is usually enough to ensure that the person knows they are part of the effort.

However, for this NDC RFA, we are requesting letters from everyone.

APPENDIX

Nanomedicine Roadmap Matrix

High Risk

(7) Initiate simple early attempts to manipulate biological nanosystems *in vivo***:** Control, modulate, divert existing cellular machinery.	**(8)** Develop strategies and fabrication methods, and use them to build synthetic and/or hybrid nanostructures, assemblies and systems using rules learned.	**(9)** The long-term goals are to autonomously manipulate biology's nanosystems within living cells to improve health by engineering tools to interface with nanostructures in living systems, e.g., (i) Design nanoparticles for "search and delivery" -Search for early disease signatures -Deliver therapeutic agents to affected cells (ii) Design nanostructured organelles to replace or augment faulty nanosystems and restore function.
(4) Make high resolution *in vivo* measurements, including dimensions of time and movement, for individual molecules and assemblies.	**(5)** Identify and define rules (underlying design principles) for self-assembly and disassembly of natural nanostructures and complexes. Implement training programs at all career levels, including senior fellowships, designed to create a new breed of investigator who is rooted in biology and also skilled in the rigorous, in-depth, physical and quantitative methods required to envision new designs in engineering.	**(6)** Discover biological nano-networks, interacting machines, supramolecular assemblies, and increasingly complex nanosystems. Discern emergent properties. Develop design principles for assembly and function of nanoscale devices for biomedical use, based on information from nature's nanosystems – biological molecules and assemblies.
(1) Identify and understand physical characteristics of molecular machines and assemblies for biological model systems. Develop a lexicon to describe biomolecular processes in engineering terms. Set up initial data systems. - Initiative 1: Workshops to plan for Nanomedicine Centers, including a data center. - Initiative 2: Nanomedicine Development Centers	**(2)** Develop new physical methods/tools for *complete* biophysical characterization of biological model systems initiated in Box 1. Refine computational tools for data collection, storage, analysis and dissemination. Incorporate additional biological model systems as appropriate.	**(3)** Complete a physical and biochemical description/catalog of all known molecular assemblies and machines. Create a comprehensive national data resource and information clearinghouse with public access to information on tools, measurement standards, and characterized biological systems. The Centers program will mature as centers compete and form a national network that produces and analyzes comprehensive biophysical data on biomolecular systems, and provides user resources and training.

Low Risk

Short Time → ***Long Time***

Nanomedicine Roadmap Matrix Supporting Text

Introduction: Nanomedicine is a broadly-used word that describes the interface of biology to nanotechnology in a context of understanding and treating disease. For our purposes, nanotechnology as applied to biomolecular systems is accomplished through the quantitative description of cellular processes. This requires characterizing these systems by their physical properties (e.g., force, stoichiometry, kinetics, material requirements, energy utilization and transduction). The key challenge is to develop physical descriptors of biological systems that allow seamless integration of biosystems concepts with engineering, to reveal the design principles underlying biology. Understanding those design principles will allow us to address two complementary goals central to the NIH mission. First, the biological basis of health and disease will be better understood, enabling us to choose the most effective points at which to intervene in disease processes. Second, we will be able to create blueprints for the design of new nanomachines or structures for health monitoring and maintenance, and disease detection and treatment, that will be more sensitive and specific than ones based on qualitative descriptions of biology. In addition to achieving those two goals central to NIH's mission, a third outcome will benefit nanotechnology more broadly, in that other science and engineering disciplines will receive information on design concepts that have been tested and proven to work by the experiments nature has conducted.

The research needed to achieve these goals, including maintaining focus on important medical problems, requires a confluence of disciplines and input from across the NIH.

Box 1: **Identify and understand physical characteristics of molecular machines and assemblies for biological model systems.**

Biomolecules are nanometer-scale structures. Existing technologies will be employed to describe and to catalogue – in physical, chemical and mathematical terms – the nature of known biological nanostructures, assemblies, and machines. The goal is to move from descriptive data to quantitative analyses such that each system can be fully understood using objective physical parameters such as force, stoichiometry of subunits, kinetics, material requirements, energy utilization and transduction. *Collecting this comprehensive data set requires a coordinated effort to develop uniform standards, a lexicon of engineering terms and definitions applicable to biological processes and structures, and data systems to collect and analyze the data.* As we develop this lexicon we will discover gaps in our ability to collect essential data. To complete the analyses, new tools and strategies will be discovered and applied. The endpoint of this activity will be a characterization of biomolecular systems in a format that will interface seamlessly with engineering specifications required to create blueprints for the design of new nanomachines or structures.

This analysis is focused initially on a set of model systems (to be identified during the planning process) that serve as demonstration projects. Examples of the types of model systems that might be chosen and themes to be addressed include:

- Transport: Membrane transport via pores or gates
- Information transfer: Virus-cell interaction and cell signaling cascades
- Energy transduction and utilization: mitochondria and molecular motors
- Information conversion: Transcription/translation -- ribosomes, RNA polymerases

Meeting these goals depends on sustained support for interdisciplinary teams composed of physicists, biologists, chemists, engineers and computational scientists. These collaborations can be effectively pursued by creating Nanomedicine Development Centers that conduct the research and provide expertise and instruments as well as a substantial service or user facility. Additionally, these centers will form the nucleus for integrative training for students of all ages and career levels. The science supported by these centers cuts across NIH Institute and Center missions; funding and management will require partnerships.

Box 2: Develop new physical methods/tools for *complete* biophysical characterization of biological model systems.

Having learned which measurements are crucial and what additional tools are needed, the focus will be to develop and apply those tools to complete the analysis of the representative molecular machines and assemblies. Refinement of computational tools for data collection, storage, analysis and dissemination is also high priority. Several other potential model biological systems not previously addressed (e.g., chaperonins, hair cell motility, DNA packaging/chromatin) may be incorporated, to ensure that tools and concepts apply more broadly than to the initial model systems.

Box 3: Complete a physical and biochemical description/catalog of all known molecular assemblies and machines.

Activities piloted in the first two phases will be scaled to produce data for all known biological molecular assemblies and molecular machines. A comprehensive national data resource and information clearinghouse will provide public access to information about the available (wet lab and computational analysis) tools, measurement standards, and characterized biological systems. This data resource will be focused on nanobiology and medicine and will have links to databases for engineered nanosystems.

The Nanomedicine Development Centers will compete for scale-up and operate as a coordinated network. They will be the major data production and analysis centers for this project as well as national resources. They will have a service component to provide extraordinary tools to the rest of the research community. They will also incorporate integrative nanomedicine training grants funded by a trans-NIH initiative.

Box 4: Make high resolution *in vivo* measurements, including dimensions of time and movement, for individual molecules and assemblies.

The goal of these projects will be to make high-resolution measurements *in vivo*, where interactions between different systems can lead to changes in the behavior of the individual nanomachines and nanosystems. The relevant interactions are between multiple "copies" of a system carrying out related functions (e.g., multiple ribosomes translating the same mRNA and different mRNAs; or a regulated array of microtubules forming a dynamic cytoskeleton), and between different systems that interact (endo/exocytic pathways with signaling pathways with cytoskeleton with translation machinery, to name just a few). The challenge is to describe behavior of this army of nanomachines in statistical terms. It will be necessary to measure both the behavior of particular instances of a nanomachine and the random variation in behavior across time and across identical assemblies. Because molecular behavior has a random component simultaneous measurement of multiple parameters will be needed to characterize covariance of parameters.

A related goal is to develop systems for real time data capture and analysis that support multiple measurements simultaneously. Real-time data capture is an essential component of closed-loop (measurement-to-response) systems.

Box 5: Identify and define rules for self assembly and disassembly of natural nanostructures and complexes.

Algorithms to relate multiple single-molecule measurements to ensemble behaviors will be developed. Integrated models of assembly behavior will be generated. The goal will be to describe the directed, regulated self-assembly of biological nanosystems in physical and quantitative terms, including energy requirements and information transfer. Insight into possible methods to manipulate the self-assembly process will emerge, leading to concepts for switches or sensors that could be developed to control the process, and to design principles for building nanoengineered devices.

In the context of this goal, training of future researchers in nanoscience/nanotechnology will be invigorated. Re-education of academic biological scientists is needed to achieve greater emphasis on quantitative thinking. Training programs at all levels, including senior fellowships, are needed to create a new breed of investigator who is rooted in biology and also skilled in the rigorous physical and quantitative methods required to envision new designs in engineering.

Box 6: Discover biological nano-networks, interacting machines, supramolecular assemblies, and increasingly complex nanosystems.

Novel computational methods involving modeling and simulation, using inputs from physical measurements, will reveal previously unrecognized links and interactions between components (molecules, assemblies and networks). Higher-level system properties (emergent properties) will also be revealed by these analyses. Box 3 activities will be adjusted to incorporate measurements on these additional interactions and system properties.

Box 4 activity, to identify rules and design principles for self-assembly, will be extended to higher-order levels of system organization.

Emerging design principles based on biology, along with fabrication strategies and methods developed in Box 8, will be used to design and implement engineered nanostructures for controlling biomolecular processes. These nanostructures may incorporate biological and non-biological components (i.e., hybrid nanodevices).

Box 7: Initiate simple early attempts to manipulate biological nanosystems *in vivo.*

The goal is to manipulate (control, modulate, divert existing cellular machinery) nanosystems *in vivo* using versions of the methods and tools that are used for measurement. The biological systems that will be manipulated are ones on which sufficient data are available that meaningful measurements of perturbations can be made. Starting from manipulation and measurement of individual biomolecules, the studies will progress to supramolecular assemblies (measuring the effects of manipulating one component of the assembly on other components), and then to manipulating and measuring different components of a network.

Box 8: Build synthetic and/or hybrid nanostructures and assemblies using rules learned.

With an emphasis on synthesizing or constructing devices whose designs mimic biological systems, the knowledge and information gained from experiments on manipulating biological nanosystems *in vivo* becomes crucial. Here, a more significant participation and leading role by researchers with expertise in chemistry and engineering in particular is anticipated. Whereas the tools used in Box 7 are mostly not themselves nanoscale devices, efforts will be made to build both synthetic and/or hybrid nanostructures and assemblies that can, in turn, be used to manipulate biological molecules and assemblies. This is obviously very challenging. Along the way, devices and systems that are not themselves nanoscale devices, but that have nanoscale components and can be used for health-related purposes, will be developed. Examples include the use of biological motor proteins to actively transport cargo in Microelectromechanical Systems (MEMS) devices (e.g., for use as implantable drug pumps), and improvement of molecular and biomolecular modified Field-Effect Transistors (FET) for microbiosensors that are either ion-sensitive, or based on enzyme/receptor-ligand interactions, etc. These capabilities would enable development of closed loop (sensor-actuator) systems for measured therapeutic delivery.

Box 9: Remotely manipulate nanosystems in living cells; engineer tools to interface with nanostructures in living systems.

The long-term goal of this research is to develop the ability to rationally control, modulate or divert existing nanosystems for therapeutic purposes. The insight gained from the complete quantitative understanding of biological nanosystems will lead to the identification of *design principles* that will guide the engineering of new tools to interface with living systems. The

rational design of diagnostic and therapeutic nanosystems based on biological design rules is ideally suited for the development of tools for nanomedicine since materials in this size range are on the same scale as cellular substructures and organelles. Examples of classes of technology that could be designed to address disease are (i) tools for "search and delivery" to carry out site-specific delivery of therapeutic agents, or (ii) nanostructured organelles to replace or augment defective cellular machinery and restore function:

Nanoparticles for "*search and delivery*" could be designed to:

- Search for early disease signatures of affected cells, through recognition of cell surface markers, in cancer, vulnerable plaque, viral infection, T-cell invasion of islets, inflammation, as examples;
- Deliver to affected cells a therapeutic agent to modify or kill cells, a signal to recruit cellular degradation machinery, or a mechanism to inhibit proliferation of affected cells;
- Perform dual role of site-specific targeting and delivery by specific engineering of novel nanoparticles.

Nanostructured organelles to *restore function*:

In Parkinson's Disease, for example, organelles could be delivered to affected cells to:

- Replace the ubiquitin proteasomal degradation system to remove parkin substrates
- Replace or enhance chaperone activity to delay degeneration induced by α-synuclein
- Deliver fresh mitochondria-like particles to diseased cells to delay degeneration.

Whether the biomedical goal is *search and delivery* or *restoration of function*, the nanoparticle will be designed to deliver a specific function to an affected cell, in a measured response. The nanoparticles may be entirely manufactured or may be derived by co-opting other cellular functions to generate new therapeutic tools. Mimicking the design of biological systems, these diagnostic and therapeutic systems will be self-directing, self-organizing (multiple nanodevices working in concert, under active feedback control), self-repairing (or self-inactivating if repair is impossible), and self-sufficient (incorporating energy sources or energy regeneration capacity).