NSF Workshop Report on

Re-Engineering Basic and Clinical Research to Catalyze Translational Nanoscience

University of Southern California, Los Angeles, CA
16-19 March 2008

Sponsored by National Science Foundation

James S. Murday, University of Southern California, Workshop Chair
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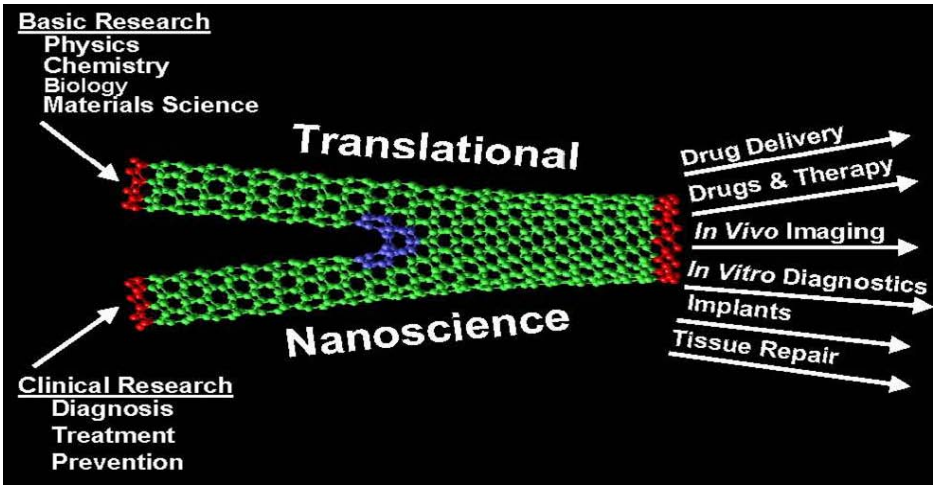

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On

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University of Southern California
Los Angeles, California

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Cover Figure: Schematic representation of interaction between the physical science/engineering communities with the medicine/health communities in order to accelerate the translation of nanoscience discovery into clinical applications.

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Translational Nanomedicine: Status Assessment and Opportunities

James S. Murday, University of Southern California; Richard W. Siegel, Rensselaer Polytechnic Institute; Judith Stein, General Electric Global Research; J. Fraser Wright, Children's Hospital of Philadelphia and University of Pennsylvania

I. Introduction

Nanostructures and their properties are critical to understand and develop innovations in biological systems, therapeutic agents, and medicine and health. However it has only been in the last five years that "nanomedicine" as a field has been created and has rapidly accelerated. This paper explores the reasons behind that fact, examines the science and engineering issues that remain to be addressed if one is to more rapidly translate nanoscience discovery into nano-enabled medical technology, and suggests Federal agency actions that could accelerate that eventuality.

The U.S. National Nanotechnology Initiative was instituted in 2001 to accelerate and exploit progress in the science and engineering of nanostructures. As evident in Figure 1, exponential growth in literature addressing the nanoscale began about 1990. Interest in the nanoscale has been driven by the commercial availability of nanoscale manipulation and characterization tools, the expectation of new physical, chemical, and biological properties of nanostructures, the expectation that nanostructures will provide new building blocks for innovative new materials with novel properties, the miniaturization into the nanoscale by the semiconductor industry, and the recognition that the molecular machinery in a biological cell functions at the nanoscale. Historically, aspects of chemistry and biology - such as colloids, protein engineering and molecular virology - have involved nanostructures, but on a largely empirical basis. Finally, there is an expectation that a better understanding of the 1-100nm materials size scale (the nanoscale) will lead to a seamless integration of theory and models across the size scales that encompass atomic-molecular-nanostructure-microstructure behavior and thereby enable the *a priori* prediction and design of a material's properties.

The nanoscale literature in the 1990s is dominated by investigations of "hard" materials – ceramics, metals, semiconductors - only in small part due to the keen interest in nanoelectronics devices. Many of the new nanoscale analytical tools depend on proximity between a tip and the sample under investigation. This requirement was not overly onerous for relatively stiff materials, the primary focus of nanotechnology in the 90s. In contrast, soft materials, those of predominant interest in the biology and medical communities, are more readily deformed by a proximal probe and are thereby more difficult to analyze quantitatively. It wasn't until roughly 2000 that improvements in commercially available instrumentation made the analysis of soft material more viable. Not coincidently, the literature reporting nanostructures in biology, medicine and health began to increase more rapidly at that point (see Figure 1).

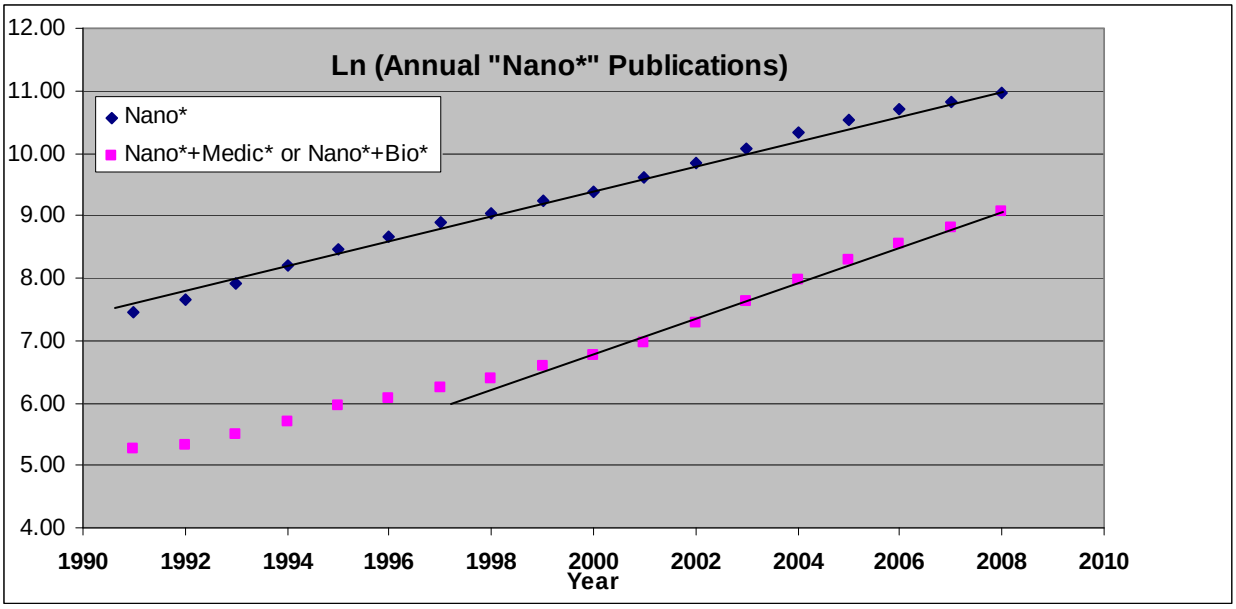

Figure 1: Publication counts derived from the Thompson ISI Web of Science database on 3/15/2009 using the indicated keywords. The vertical axis is the natural logarithm of the number of publications. There is a clear change in slope for the publications associated with biology and medicine around the year 2000.

The increase in research activity has to be complemented by programs in the various funding entities. For example, in the U.S. there are eleven agencies with nanoscale research and development (R&D) programs reported by the U.S. National Nanotechnology Initiative (NNI, see Table 1) [1, 2]. The reported funding for nanoscale science and technology has grown by nearly a factor of 4 since the initiation of the NNI in 2001.

Table 1
U.S. Federal Agency R&D Funding in the NNI

	FY2001 requested*	FY2001 actual*	FY2005 requested*	FY2005 actual*	FY2009 requested*
NSF	217	150	305	335	431
DOD	110	125	180	352	397
DOE	94	88	211	208	311
HHS (NIH, NIOSH)	36	40	89	168	232
DOC (NIST)	18	33	53	79	110
NASA	20	22	35	45	6
EPA		5	5	7	5
USDA (CSREES, FS)			5	2	8
DOJ			2	2	2
DHS (TSA)			1	1	1
DOT (FHWA)					1
Total		~460		~1200	~1500

* The Presidential Budget submission presents requested funding; actual funding is reported by the agencies after the end of the fiscal year. The differences reflect Congressional appropriation decisions, including Congressional adds, and agency funding decisions taken during the fiscal year.

At the beginning of the NNI, the National Institutes of Health (NIH) investment at the nanoscale was modest. The NIH hosted two workshops - Nanoscience and Nanotechnology: Shaping Biomedical Research, June 2000 [3], and Nanobiotechnology, October 2003 [4] - to better understand the potential impact of nanostructures on medicine/health and the knowledge deficiencies inhibiting progress. These workshops, along with promising results from research [5], led to major increases in the NIH investment in nanoscale research. The nanoscale investment by NIH has more than doubled since 2005 (sextupled since 2001 – see Table 1).

As part of the NIH investment to exploit the nanoscale, Nanomedicine was incorporated into the NIH Roadmap for Medical Research in 2004 [6]. Understanding nanoscale properties permits engineers to build new materials structures and use these materials in new ways. The same holds true for the biological structures inside living cells of the body. To meet the challenges, and complement its Institute-based programs, the NIH established a national network of eight Nanomedicine Development Centers. These collaborative centers are staffed by multidisciplinary research teams including biologists, physicians, mathematicians, engineers and computer scientists. In the initial phase of the program (FY2005-FY2010), research has been primarily directed toward gathering extensive information about the chemical and physical properties of nanoscale biological structures.

The European Science Foundation launched a Scientific Forward Look on Nanomedicine in 2004, which involved a series of five workshops and a Consensus Conference (Nov 2004). This was followed in Nov 2006 by a report with a strategic research agenda for nanomedicine [7]. Founded in 2007, the European Society of Nanomedicine [8] shares office space with the European Foundation for Clinical Nanomedicine (CLINAM foundation) [9]. The first European Conference for Clinical Nanomedicine was organized by CLINAM in May 2008 and had sessions on unsolved problems waiting for nanomedical solutions, nanotechnologies at hand for solving medical problems, clinical trials in nanomedicine, and building bridges between clinicians and nanoscientists. A proceedings from the NATO Advanced Research Workshop on Nanomaterials for Application in Medicine and Health has been published [10].

The growing attention to nanostructures in medicine/health is also reflected in the professional science and engineering communities. A Handbook of Nanomedicine is being implemented [11]. The American Academy of Nanomedicine, founded in 2005, launched a journal - Nanomedicine: Nanotechnology, Biology and Medicine (ISSN1549-9634). The Institute of Nanotechnology, founded in the UK in 1994, began its nanomednet [12] in 2007. Additional journals, the International Journal of Nanomedicine (ISSN 1176-9114) and Nanomedicine (ISSN 1743-5889) were both launched in 2006. While not strictly "nano," another relevant journal is the Royal Society of Chemistry's Lab on a Chip [13] initiated in 2001. The American Physical Society PACs classification scheme has been modified to include "nanotechnology design" (87.85.Qr) and "nanotechnology application" (87.85.Rs) under Biomedical Engineering (87.85). Recurrent professional forums addressing aspects of nanomedicine are: The International Nanomedicine and Drug Delivery Symposium (NanoDDS – began in 2003) [14], the Annual Meeting of the American Academy of Nanomedicine (began in 2005) [15], the Society for Biomaterials meeting [16], the AVS International Symposium and Exhibition [17], the European Science Foundation conference Nanomedicine 2008 [18], and the International Conference on Biomedical Applications of Nanotechnology [19].

The paucity of knowledge for nanostructure impact on environment, safety, and health (ESH), coupled with the growing prevalence and diversity of, and especially the novel engineered properties in, nano-enabled technologies continues to raise ESH concerns [20]. Knowledge of nanostructure ESH risks and their amelioration will be symbiotic with health and medicine applications since understanding how to avoid health problems can potentially be used to guide therapy and *vice versa*. Workshop and task force reports on ESH issues include: Nanotechnology: A Report of the US Food and Drug Administration [21], and Environmental, Health, and Safety Research Needs for Engineered Nanoscale Materials [22], a UK report on Nanomaterials risk [23], an International Council on Nanotechnology (ICON) report [24], and a European Commission paper [25].

Conventional wisdom, buttressed by observation, posits a 20 year gestation period between science discovery and its exploitation in the market. Figure 2 illustrates this point for several major 20th century technologies, and suggests imminent emergence of nano-enabled technologies. In practice, nanostructures have been utilized in selected technologies for some time, including carbon black in tires, colorants in stained glass windows, colloidal silver as a disinfectant, colloids and colorants in cosmetics, and many catalysts. Small particles have also been in use for biomedical research and *in-vitro* diagnostic protocols during the last fifty years [26, 27]. Most of these applications are based on technology derived empirically from macroscopic observations.

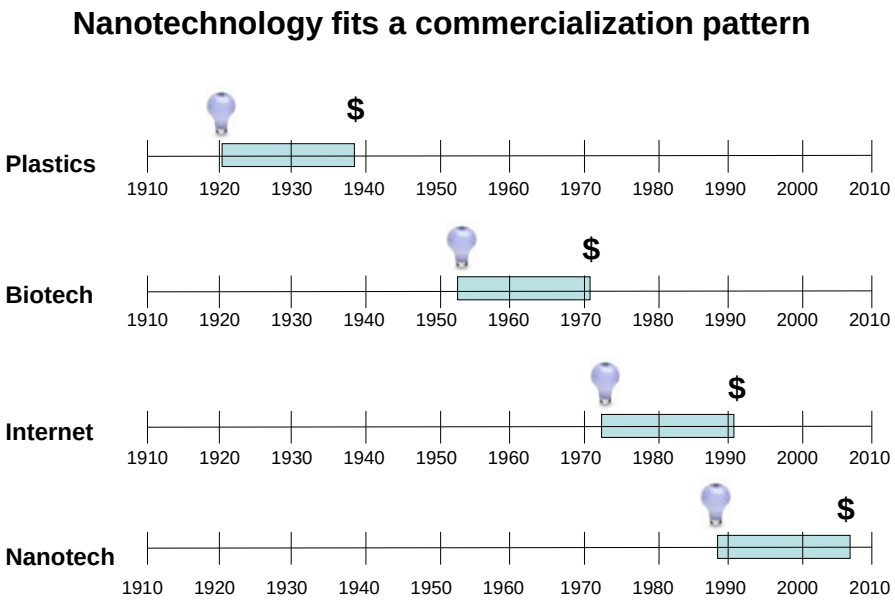

Figure 2: Time required for maturation of science discoveries into commercial products. Courtesy Lux Research Inc. • One Liberty Square, Suite 210, Boston MA 02109

There is a database with a listing of products in the market that are (or claim to be) nano-enabled [28]; there are also specific listings of nano-enabled products in medicine and health [29, 30]. As the capability to make, measure, and manipulate individual nanostructures continues to

progress, one can expect more extensive entry of nano-enabled and nano-enhanced products and technologies into the marketplace in the coming years.

While twenty years might be the generic interval for transition of science discovery to innovative technology to translation of these technologies into medical applications, a thoughtfully crafted investment strategy might shorten this time frame. To improve human health, scientific discoveries must be translated into practical applications. Such discoveries typically begin at "the bench" with basic research — in which scientists study disease at a molecular or cellular level — then progress to the clinical level, or the patient's "bedside". Scientists/engineers are increasingly aware that this bench-to-bedside approach to translational research is really a two-way street [31]. Basic scientists provide clinicians with new tools for use with patients and for assessment of their impact; clinical researchers make novel observations about the nature and progression of disease that often stimulate basic investigations. Translational research has proven to be a powerful process that drives the clinical research engine [32]. However, a stronger research infrastructure could strengthen and accelerate this critical part of the clinical research enterprise. Through discussions with deans of academic health centers, recommendations from the Institute of Medicine, and meetings with the research community, the NIH recognized that a broad re-engineering effort is needed to create greater opportunity to catalyze the development of a new discipline of clinical and translational science. An outcome was the launch of the Clinical and Translational Science Awards (CTSA) Consortium in October 2006.

Accelerating discovery into technological device is certainly a goal for the DOD hierarchy of research and development funds (evolving from basic (6.1), applied (6.2), advanced technology development (6.3), advanced component development and prototypes (6.4), to system development and demonstration (6.5)) and the NASA research and development funds evolving from technology readiness levels 1 through 6. One might consider the NIH equivalent as R01 programs to explore new concepts (basic), the R21 programs to demonstrate feasibility (applied research), the R33 programs to further develop the idea toward a technological/methodological goal, and the Clinical and Translational Science Awards (CTSA) providing translation into the clinic (which might be considered the equivalent of initial field testing by DOD or NASA).

Many agencies, NIH included, also utilize SBIR/STTR and public-private partnerships as a bridge into commercialization. In contrast to many DOD/NASA technologies, because there are large public markets for medical/health technologies, commercialization does not have to rely as predominantly on additional Federal funding.

The April 2008 report on the NNI by the Presidents Council of Advisors on Science and Technology (PCAST) emphasizes the central role the NNI must play in overcoming the barriers to nanotechnology development and commercialization [33]. The 2009 U.S. NNI reauthorization draft bill (H.R.554, 111th Congress) also places greater emphasis on applications. As a key supporter of nano-bio basic research, NSF sponsored a workshop on Re-Engineering Basic and Clinical Research to Catalyze Translational Nanoscience on 16-19 March 2008, hosted by the University of Southern California, with a goal to provide insights toward a Federal government nanomedicine investment strategy. The workshop participants, listed in Table 2, were carefully chosen to reflect both individuals working in nanoscience and nanoengineering

and those working in clinical settings. The NIH - Institute of Biomedical Imaging and Bioengineering (NIBIB) sponsored a conference (20-21 March 2008) to present the preliminary findings.

Table 2: Workshop Participants

Name	Institution
Mark Braganza, MD	Texas Pacific Group Growth
Tom Buchanan, MD	University of Southern California
Wah Chiu, PhD	Baylor College of Medicine
Vicki Colvin, PhD	Rice University
Richard Cote, MD	University of Southern California
William Galey, PhD	Howard Hughes Medical Institute
Martha Gray, PhD	Harvard University
James Heath, PhD	California Institute of Technology
James Hone, PhD	Columbia University
Mark Humayun, MD, PhD	University of Southern California
Anupam Madhukar, PhD	University of Southern California
Ellis Meng, PhD	University of Southern California
Michael Roukes, PhD	California Institute of Technology
Jeffrey Schloss, PhD	NHGRI, NIH
Richard Siegel, PhD	Rensselaer Polytechnic Institute
Judith Stein, PhD	General Electric Corporation
Edwin Stone, MD, PhD	University of Iowa
Samuel Stupp, PhD	Northwestern University
Sally Tinkle, PhD	NIEHS, NIH
Fraser Wright, PhD	Children's Hospital of Philadelphia and Univ Penn.
Steven Moldin, PhD	University of Southern California
James Murday, PhD	University of Southern California

Based on information derived from the workshop and other resources, the succeeding sections of this report will examine opportunities to accelerate the development and optimization of nanostructures for impact on medicine and health. The next section briefly explores economic and societal drivers for nanomedicine initiatives. The third section will examine the science, engineering, and medical research needs. The fourth section succinctly examines the U.S. Federal investment directly germane to medicine and health, with brief mention of the European Union (EU) effort. The final section presents recommendations to accelerate the translation from laboratory discovery into clinical practice.

II. Healthcare Needs with Promising Nano-enabled Technology Impact

An investment strategy to accelerate nanoscience into nano-enabled technology for medicine and health should reflect both health need (technology pull) as well as science push. Within this context, science and engineering of nanoscale structures is expected to make major contributions across the entire medicine and health spectrum ranging from mortality rate, morbidity an illness imposes on a patient, disease prevalence, and general societal burden [29, 34-36]. The following

examples illustrate potential economic and therapeutic impacts, even if nano-enabled technologies only contribute partial solutions:

- The direct medical cost for cancer in the U.S. for 2007 was about $90B [37]. The National Cancer Institute has recognized the importance of nanostructures in the diagnosis and treatment of cancer in its Alliance for Nanotechnology in Cancer (http://nano.cancer.gov/). Nanotechnology approaches [38] are progressing rapidly in: early diagnosis [39-41], nano-enabled contrast agents for in-vivo imaging [42-47], nano-reformulations of chemotherapy agents for lesser quantities of drug, targeted delivery for smaller side-effects [48-52], and new treatments such as nanoparticle-mediated tumor ablation [5, 53].

- The direct medical cost for diabetes in the U.S. for 2007 was about $116B [54]. Nanotechnology approaches to *in-vivo* monitors of glucose levels [55, 56] and production of insulin [57] are being explored.

- The annual medical care cost for spinal cord injury in the U.S. is about $1.5B; the full costs are estimated as about $10B/yr [58, 59]. There are promising nano-enabled approaches to the regeneration of spinal neurons, a capability once thought impossible [60, 61].

- In the US, in order to remain physically active, approximately 200,000 people receive hip implants and 300,000 people receive knee implants [62]. The average life-time of current orthopedic implants is only 10 – 15 years; revision surgeries and their recoveries are not as successful as the first operation. The cost of an implant varies but is roughly $20,000. Nano-enabled innovations in bone cement and composite structures are opening new possibilities for improvements in implants [63-66].

The 2006 "Nanomedicine: Nanotechnology for Health" publication of the European Technology Platform – Strategic Research Agenda for Nanomedicine presents additional examples of expected nanomedicine impact [67].

The workshop participants were polled for their opinion of pressing clinical needs amenable to nano-enabled technology and identified the following as illustrating the wealth of opportunities:

- Intelligent nanobiomaterials for cell therapy to improve heart function
- Safe and affordable therapeutic strategies to regenerate neural tissues
- Kidney – hollow fiber membranes
- Detoxification implants- correction of metabolic disorders
- Cochlear and retinal implants
- New power source technology for implants
- Repair articular cartilage and regain homeostasis with the joint
- Skin regeneration
- Anti-microbials
- Drug delivery with
  - Targeted pharmacotherapy – tissue/organ
  - Therapeutic DNA transfer vectors

- Nanoparticle (NP) to carry a therapeutic payload across the blood brain barrier
- Transfection devices for therapeutic uses.
- Controlled release (especially long term, continuous and programmed)
- Transient application – sonoporation and electroporation

III. Nanoscale Science and Engineering Research Needed to Enable More Effective Technology

The considerable investment in nanoscience across the world has been leading to many new discoveries. In the second five years of the U.S. National Nanotechnology Initiative there is growing effort to identify potential applications for those discoveries and to accelerate their transition into innovative technology solutions to societal problems. Medicine and health provide fertile ground for this goal. For convenience, this section is organized about the headings of Diagnostics, Drugs, and Therapy, Implants and Regeneration, Systems Biology, and Medical Instrumentation and Devices. The amount of published work is growing rapidly; this paper's intent is not to be exhaustive, but rather illustrative of these topics.

IIIa. *In vivo* and *In vitro* Diagnostics

IIIa1. *In-vivo* Imaging – Contrast Agents

A number of non-invasive medical imaging approaches - such as computed tomography (CT), magnetic resonance (MR), positron emission tomography (PET), single photon emission CT(SPECT), ultrasound (US) and optical imaging (OI) - are currently being used. The emergence of nanosized contrast agents for these tools has been the subject of several recent reviews [45-47, 68, 69] and is anticipated to lead to advancements in imaging for understanding biological processes at the molecular level. Examples of these nanoparticles are biocompatible polymer-based nanogels/nanospheres/nanoemulsions, carbon nanotubes, dendimers, gold nanoparticles, liposomes, micro-bubbles, semiconductor quantum dots, silica nanoparticles with enclosed fluorescers, and superparamagnetic iron oxide particles. Generic goals for these contrast agents include:

- Signal-to-noise (S/N) enhancement to allow high sensitivity and resolution levels.
- Selective binding to target cells to provide a localized, specific enhancement.
- Long circulating half-life (hours) to expand the imaging time window.
- Acceptable toxicity profile.
- Ease of production and clinical use in order to be economically and commercially sustainable.

Nanostructured imaging contrast agents are overcoming many limitations of conventional contrast agents such as poor photostability, low quantum yield, and insufficient *in vitro* and *in vivo* stability. They are small enough to be taken up by single cells - via processes such as phagocytosis, pinocytosis or vector-mediated transport - as labels for *in vivo* imaging [42, 43]. Since the nanostructures are sufficiently small, one can envision linking them to provide multiple functions, opening possibilities for multimodal imaging, high payload of imaging reporter, activatable "on-off" systems, and chemical information. For instance, human oral cancer cells have been found to assemble and align gold nanorods conjugated to anti-epidermal growth

receptor antibodies [70]. Molecules near the nanorods on the cancer cells gave a Raman spectrum (SERS) that was enhanced, sharp and polarized; those spectral features could be used for diagnostic signatures.

Research issues and opportunities include:

- Controlling nanomaterials themselves: a) purity, b) particle size and shape, and c) size distribution (mono-dispersity) of the particles. Their characterization requires specialized laser scattering techniques and microscopies to measure particle size and overall morphology, core composition/structure techniques, and surface analysis for composition/structure of any shells. The high-end instruments necessary for this characterization may not be readily available for the normal research laboratory and may require the use of user facilities or private analytical groups.
- Exploiting new contrast mechanisms - such as nanoparticle enabled surface-enhanced Raman [68, 71-73] - for the extraction of molecular spectral information.
- Ascertain the effects of composition, size, coating, surface charge density and the attached ligands on nanostructure pharmacokinetics and biodistribution.
- Explore mechanisms to ensure that particles are not rapidly accumulated in the spleen and liver.
- Delivery of nanoparticles to the cytoplasm of live cells.
- Incorporate multiple targeting ligands for enhanced selectivity. More than one epitope may be over expressed on a cell surface at a given time, so heteromultivalent probes for diagnosis and therapeutics will likely be important to selectivity.
- Utilizing nanoparticles as building blocks to obtain multimodal functionality – such as recognition, enhanced contrast, functional imaging, and therapeutic action.

IIIa2. *In-vivo* Diagnostics (non-imaging)

As microelectromechanical systems (MEMS) become more sophisticated and miniaturization continues into the nanoscale (MEMS evolving into nanoelectromechanical systems, NEMS), it will become possible to incorporate ever more sophisticated analytical capability onto and into the human body [74, 75]. There are already a growing number of miniaturized devices for transdermal sensing. Examples include the SCRAM system which is a high-tech bracelet that samples a person's sweat to monitor alcohol ingestion [76]; Echo's Symphony™ tCGM System which is a non-invasive (needle-free), wireless, transdermal continuous glucose monitoring (tCGM) system [77]; and Flexible Medical Systems, which is testing a MEMS chip with readable via RFID technology that could be applied to the skin via a band-aid to sense body fluid constituents [78]. As miniaturization continues, enabling greater sophistication per unit volume, the variety of measured analytes (and other properties such as temperature, tissue turgidity, etc.) will certainly increase. It is also within the realm of possibility that "spectrometers-on-a-chip" will be developed for insertion beneath the skin.

Research issues and opportunities include:

- Continued miniaturization for more sophisticated sensing of medically relevant parameters, including nanostructures for sensitive and selective transduction of biological events into electrical signals.

- Development of more effective wireless communications and power delivery suitable for the human body and human body exposures.
- Additional items as listed in Section IIIc, Implants.

IIIa3. *In-vitro* Miniaturized Diagnostics

Current approaches to medical diagnostics are usually high-cost, bench-top laboratory analyzers, or disposable kits that only test for a single analyte. The challenges are considerable when determining whether sophisticated chemical/physical laboratory instrumentation can be reduced in size, while retaining adequate capabilities. For instance there are 10^4-10^5 different proteins in blood with concentration ranges from 10^{-3} to 10^{-17}M. Miniaturized chip-based, array detection methods, known as microarrays, have been prevalent in almost all areas of health-related research for some time; continued miniaturization into nanoarrays will generate many orders of magnitude increase in multiplexed detection [79, 80]. Further, as noted in the section on contrast agents, nanoparticles are already incorporated into some diagnostics to provide greater selectivity, sensitivity, and practicality as compared with conventional systems.

Beyond the arrays, an alluring potential for micro/nano devices is to harness the concept of laboratory-on-a-chip for medical diagnostics [81-92]; analytical microchips are considered to be a fast growing technology [93]. The lab-on-a-chip concept (incorporating microfluidics) has several features that have attracted users in biology, chemistry, engineering and medicine. It requires only small volumes of samples and reagents, produces little waste, offers short reaction and analysis times, is relatively cheap, and has reduced dimensions compared with other analytical devices. Potential applications include: point of care measurements of saliva for periodontitis [41], heart disease [94], hemacrit determination [95], insulin detection [96], and improving healthcare accessibility [97]. In addition to improving established diagnostics, new approaches - such as mechanical analysis to distinguish cancerous cells from normal ones even when they show similar shapes [98] - will be discovered and implemented. The lab-on-a-chip concept is particularly attractive as an approach to providing inexpensive, effective medical care especially in underserved populations [40, 99, 100].

Research issues and opportunities include:

- Arrays that can carry out larger numbers of experiments in parallel to assess reproducibility.
- Separation techniques to sort body fluid constituents.
- Optical and electromagnetic technologies incorporated in chip-based devices for manipulating samples and their analysis.
- The need for improved knowledge of pertinent biomarkers so that chip technologies can be more effective.
- More robust alternatives to antibody/antigen for selectivity determination.
- The need for validated and easy to operate microfluidic platforms which give the users the freedom to easily combine the basic modules for different fluidic operations in order to build application-specific microfluidic systems [101].

IIIb. Drugs, Delivery, and Therapy

IIIb1. New Approaches to Drug Development

There is need to analyze potential drug candidates in a more rapid and accurate manner, a need that provides an opportunity to develop new tools for that purpose. Ideally, to provide specific information, quantification of single cell pharmacokinetics/dynamics is desired, but requires the detection of minute quantities of proteins and other molecules [102]. One must identify and evaluate types of drug targets (including proteins, polysaccharides, lipids and nucleic acids) that can interact with small-molecule therapeutic agents. Polysaccharides, lipids and nucleic acids have been investigated less frequently than proteins, because of a lack of understanding of the involvement of these molecules in disease and a lack of small molecule therapeutic agents.

Traditional high throughput systems (HTS) perform by using multiple-well plates. Microfluidic technologies, and their nano-enabled enhancements, have great potential in high-throughput studies involving target selection, lead compound generation, identification, and dosage design.

In general, in-vivo imaging has been focused at the diagnostics level and has not been an inherent component of drug discovery. In the past decade a paradigm shift has occurred; imaging is now adding a new dimension to our understanding of basic biological and pharmacological mechanisms [103]. Many aspects of drug development can be facilitated using molecular imaging as an integrative tool to discover new "druggable" targets, identify novel drug candidates and validate their potency, sensitivity, specificity, PK, PD and toxicity, metabolism and adverse drug-drug interactions in living systems. Clinical, epidemiological and bioinformatical data suggest that population-wide genetic polymorphism may dictate the responsiveness to molecular therapy. Novel drugs are envisioned to be specifically tailored to selected patients.

While the greatest use of nanotechnology to date has largely been in passive carriers for drug delivery (see next section), nanoparticles themselves hold potential as therapeutic agents [104, 105]. To date, about ten years after the regulatory approval of liposomally encapsulated doxorubicin to treat various forms of cancer, "higher functionality" nanoparticles such as gene transfer vectors are in the investigational new drug stage of clinical research [106]. On the horizon is the use of nanoparticles themselves as drugs – as truly active "nanomedicines".

Research issues and opportunities include:

- Continued miniaturization of microtiter plates to expand the number of materials being evaluated.
- Dispensing nanoliter volumes of liquid into the wells.
- Microfluidic devices for drug screening that are sufficiently simple and highly versatile to enable their use in both academic and industrial pharmaceutical labs.
- Drug screening chips that incorporate living cells.
- Tailored nanoparticles as drugs

IIIb2. Innovative Drug Delivery

Nanotechnology advances are the cornerstone of a paradigm shift in targeting and safely delivering agents - thereby improving controlled drug release, improving patient safety and compliance, and reducing side effects [107-112]. Through the use of colloid chemistry – e.g., liposome and micelle encapsulation – nanoparticles have been used for drug delivery for decades. Examples of nanoscale delivery vehicles now under investigation include polymeric particles [113, 114], dendrimers [48, 115], nanoshells [116, 117], liposomes [51, 118], and magnetic nanoparticles [26, 119]. There are a number of new delivery platforms in clinical trial including: a dendrimer-derived microbiocide (i.e. VivaGel, Starpharma) for HIV or genital herpes in its final stage of Food and Drug Agency (FDA) approval [48], and a dendrimer-based targeted delivery of chemotherapeutic drugs and an apoptotic sensor in cancer cells [120]. Nanoparticles also show considerable promise for drug delivery to the retina and for powering prosthetic "artificial retinas" [121]. Various gene delivery systems based on nanoparticles have been developed and different polymers have been tested as gene delivery agents [122]. Going beyond simply carrying a drug, the development of "smart" nanoparticles is an exciting and promising area of investigation, [39, 49, 52, 123-125].

Delivering intravenous agents to their intended targets is no easy task. For intravenous infusion it is estimated that only approximately one of every 100,000 molecules of agent reaches its desired destination. The generic requirements of delivery systems are [49]:

- Biodegradability and biocompatibility.
- Stability under the *in vivo* conditions.
- In the bloodstream, it must be withdrawn from the circulation where the pathology is located, to reach elevated drug concentrations in the target cells.
- Allow sustained release of the drug, to achieve therapeutic levels at the site of pathology over long periods of time.
- Prevent the drug from manifesting its pharmacological and toxicological actions until present at the site, hence decreasing the incidence of side effects.
- Prevent premature degradation of the encapsulated drug and also immunological reactions.
- Minimize resistance due to low drug permeation levels in bacteria and phagocyte cells.

Nanoscale building blocks provide opportunity for multifunctional packaging small enough to navigate body vessels and membranes. A multifunction approach is needed to circumvent the body's natural defenses or biobarriers, which act as obstacles to foreign objects injected in the blood stream. One must avoid them being removed from circulation by monocytes and macrophages or accumulated in the organs of the reticulo-endothelial system (RES), especially the liver and spleen. For instance, for many cancers endothelial gaps in tumor vasculature are measured in hundred of nanometers rather than in tens of nanometers. In this case, nanocarriers in the appropriate size range could more selectively extravasate into a tumor and provide a passive means for selective delivery [126]. Other factors influencing the magnitude and pattern of tumoral distribution are [127]: *in-vivo* stability, particle size, surface charge, and intracellular uptake.

In most cases active selectivity will be desirable. Targeted drug delivery carriers are being functionalized with antibodies or antibody fragments to provide active localization. It is well accepted that the binding affinity, stability, and size of the ligand play a critical role for successful targeting. The conjugation of multiple antibodies to each nanocarrier enhances their avidity, and nanocarriers can be surface functionalized with multiple distinct antibodies to overcome tumor heterogeneity. Peptides and antibody fragments have been developed to overcome some of the shortcomings of antibodies, and several examples of these ligands are now under clinical development. Functional, single-domain heavy chain antibodies, referred to as nanobodies, have been raised against cancer targets which either antagonize receptor function or deliver an enzyme for prodrug activation [128]. Affibodies against a variety of cancer-related targets have been developed and are now commercially available, including: EGFR, HER2, and transferrin [27].

Cancer stem cells are characterized to be a quiescent and small cell subpopulation with different surface markers than bulk differentiated tumor cells, and to present well-developed drug resistance. While there is considerable emphasis on specific cell markers in the current cancer targeting paradigm, one must also recognize cases where cell-nonspecific approaches may be necessary for more effective and consistent therapeutic output [129].

For more sophisticated applications, where greater dosage and/or actively controlled time-release is needed, MEMS/NEMS-based devices are envisioned that can incorporate both local sensing and mechanisms to dispense drugs – see section IIIc3.

Research issues and opportunities include:

- Improvements to drug storage in the nanocarrier, including increased loading capacity.
- The mechanism(s) that drives the nanocarrier toward the target.
- Approaches to surmount bio-barriers, including mechanistic understanding [130].
- Knowledge of and control over the excretion modes.
- External/internal trigger events – ultrasound, NIR, RF, pH, …– for drug release and/or intracellular penetration.
- Bioresponsive and self-regulated delivery systems.
- Improved knowledge of pertinent biomarkers.
- Novel approaches to accelerate the discovery process for multifunction nanocarriers, such as synthesis and automated screening.
- Reduce batch-to-batch variability by prefunctionalized biomaterials for the self-assembly of nanoparticles (NPs) [113].
- Defining the optimal interplay of biophysicochemical parameters that simultaneously confer molecular targeting, immune evasion, and drug release.

IIIb3. Innovative Therapy

The possibilities for innovative therapies are limitless. As one example, hyperthermia has been explored as a treatment for cancer for a couple of decades, but with limited success. Nanostructure-enabled innovation has rejuvenated hyperthermia with the nanoparticles extracting energy from near-infrared (NIR) [131, 132] or radio frequency (RF) [53, 133] electromagnetic fields. Lack of knowledge on the fundamental mechanisms involved has

slowed the implementation of clinical protocols. For instance, recent efforts [26] for elucidating the mechanisms have demonstrated that cell membrane and cytoskelton are important loci of cell damage by both ionizing radiation and hyperthermia. Technical difficulties in developing magnetic field applicators at the frequencies and field values with concurrent compliance of the safety regulations demanded for clinical use will need to be addressed.

As a second example, photodynamic therapy is also an innovative, evolving approach for treating neovascular diseases of the eye where nanostructures can play an important role [134]; two-photon infrared, nanoplatform phototoxicity has been demonstrated for rat glioma cells [135]. A third example is magnetic nanoparticles to remove toxins from the blood; however a magnetic separator suitable for real-time clearing of magnetic nanospheres needs to be improved [136]. As a final example, self-assembling nanofibers have been shown to promote neural healing after spinal cord injury [61].

Research issues and opportunities include:

1. Develop and sustain a sufficiently robust chemistry, physics, and engineering research discovery base that is effectively coupled with the biology and medicine research community so that new opportunities are recognized and quickly exploited.
2. The paucity of information on the physical/biochemical mechanisms involved in thermosensitization, including models that can describe on a microscopic basis the interplay between physical and biochemical cell mechanisms involved.
3. For magnetic nanoparticles there are different effects to be considered for power losses in physiological conditions: a) magnetic losses through domain wall displacements (in multi-domain particles), Neel relaxation (in single domain particles); and energy loss from mechanical rotation of the particles acting against viscous forces on the liquid medium [26].

IIIc. Implants and Tissue Regeneration

IIIc1. Tissue Engineering

Tissue engineering, or regenerative medicine, is an interdisciplinary field that merges principles and innovations from the physical and chemical sciences, engineering, and the life sciences. The focus on the improvement, repair, or replacement of tissue and organ function [137-140]. The ultimate goal is to enable the body to heal itself by introducing an engineered scaffold – i.e., substitute extracellular matrix (ECM) - that the body recognizes as "self." Signals are transmitted between the cell and the ECM enabling communication for cell adhesion, migration, growth, differentiation, programmed cell death, modulation of cytokine and growth factor activity, and activations of intracellular signaling. Any scaffold material must be able to interact with cells in three dimensions and facilitate communication. Scaffold pore size, pore orientation, fiber structure, and fiber diameter are known to regulate proliferation, cellular organization, and subsequent tissue morphogenesis.

Current research in tissue engineering is approaching a major breakthrough in the treatment of injury and disease due to the ability to routinely create extracellular-matrix analogous nanofibers [137]. For example, reports of nanostructure approaches to tissue engineering have dramatically

increased in the literature in the last four years (from 32 in 2004 to 219 in 2008, as identified by a literature search of ISI Web of Science using the simple keywords nanofib* and tissue). An extracellular matrix mimic must:

- Be biocompatible and function without interrupting other physiological processes.
- Not promote or initiate any adverse tissue reaction.
- Be produced by simple techniques yet versatile enough to produce a wide array of configurations to accommodate the size, shape, strength, and other intricacies of the target tissue/organ.
- Be removed via degradation of adsorption or incorporated via innate remodeling mechanisms, leaving behind only native tissues.

There are several approaches being explored for the manufacture of nanofibers for ECM such as: electrospinning [112, 141-144], phase separation [145], self-assembly [146-148], and template [149]. Each approach is different and results in a unique set of characteristics as a scaffolding system. Electrospinning is a process that can be used to fabricate scaffolds economically at large scales and can incorporate solid nanomaterials within electrospun fibers in a well-dispersed and spatially controlled manner [150]. Electrospun collagen nanofibers, for example, have been shown to produce skin substitutes with similar cellular organization, proliferation, and maturation to the current, clinically utilized model, and were shown to reduce wound contractions which may lead to reduced morbidity in patient outcomes [141]. Phase separation has generated fiber diameters in the same range as the ECM and allows for the design of macroporous structures [151]. Self-assembling peptides (SAPs) have emerged as an attractive class of 3D scaffolding materials, mainly due to the nano-scale fibrous and porous topographies that mimic the natural ECM features. Cell behavior can be controlled by cell-materials interactions if biofunctional sites are synthesized into the scaffolds [148, 152-154].

Research issues and opportunities include:

- Design nanoscale materials with functional domains that promote self-assembly into higher order scaffolds that have mechanical strength, resilience and compliance of natural ECM, while maintaining porosity and high surface area, and cues to bind circulating stem cells and then induce proliferation [154].
- Modify nanofiber properties for drug/cell recognition through the incorporation of nanoparticles and/or functionalization.
- Understand the role of nanoscale surface topography and chemistry in cell mediation through biomolecular interactions.
- Characterize the complex three-dimensional organization of the structural and functional molecules constituting the ECM .
- Incorporation of drug and gene delivery systems into biomaterial scaffolds.
- Develop and understand methods of stem cell delivery in biomaterial scaffolds overcoming the problems of cell survival.
- Biodegradable biomaterials where the by-products are bioactive agents.
- The role and efficacy of nanostructures in central nervous system regeneration.

IIIc2. Orthopedic Implants

Self-assembly and biomineralization are used in biological systems for the fabrication of many composite materials. Bone tissue is a particularly complex biological system because it contains

multiple levels of hierarchical organization. Bone has been hard to replicate, so alternative materials such as Ti alloys or composites with micro-fillers have been substituted.

The lifetime of orthopedic implants is limited primarily by implant loosening, a result of interfacial breakdown and stress [62]. Implant materials - titanium, stainless steel and cobalt alloys - are much stiffer than bone; a cement must buffer their respective mechanical properties. Polymethyl methacrylate (PMMA) is commonly used in orthopedic implant cements; without it, metal directly contacting bone leads to strong inflammatory response, and creates highly localized stresses and micro-motion of the implants. Disadvantages of PMMA include limited radiopacity, exothermic setting, and poor ossification with juxtaposed bone. The application of nanoparticles in PMMA cements, an approach that can address all of these issues, is still in its infancy. Current approaches to implant materials include creating porous surfaces [63, 155] in attempts to improve fixation, but this does not necessarily solve stiffness mismatch. Additionally, osteoblast activity can be significantly enhanced using controlled nanotopographies [156]; for instance, nanotubular titania surfaces have been shown to provide a favorable template for bone cell growth and differentiation [157, 158]. There is a published broad review on the topic of nanomaterial interactions with proteins and cells [159].

In a somewhat simpler application, new dental restorative materials already in the marketplace are exploiting composites incorporating nanoparticles of silica (for improved mechanical properties and luster) and zirconia (for improved radiopacity) in a polymer matrix [160].

Research issues and opportunities include:

- Dispersion of nanoparticles evenly in the bone cement matrix.
- Inadequate knowledge of how to engineered surfaces with nanoscale features to affect vascular and bone cell adhesion, thereby providing a bioactive surface for bone integration.

IIIc3. Implanted drug dispenser / factory

The next generation of drug delivery systems, in addition to having spatial and temporal control, is expected to be "smart" and to enable therapy that is responsive to the patient's specific needs. These advanced systems would protect drugs from environmental or biological degradation in the body, use closed-loop control to assist the patient with homeostasis, and provide autonomous drug administration. MEMS/NEMS methods can provide a sophisticated approach. With controlled delivery, appropriate and effective amounts of drug might be precisely calculated by the controller and released or manufactured at an appropriate time. Present MEMS based microfluidic drug delivery devices [161, 162] include: microneedle-based transdermal devices, osmosis-based devices, micropump-based devices, and microreservoir-based devices. Micropumps for transdermal insulin delivery, injection of glucose for diabetes, and administration of neurotransmitters to neurons have been reported [163].

The fabrication of nano- and micro-scale 3D programmable volume enclosures (voxels) to encapsulate nano-scale quantities of various materials is expected to greatly expand current capabilities. If cells/tissue are incorporated into the voxel as the drug manufacturing mechanism, the enclosure walls must have pores small enough to prevent immunoresponse, but large enough to permit the suffusion of metabolites [57]. Nanoscale approaches to power for such devices

include: stored energy (battery) [164], wireless transfer [165, 166], and local generation [167-170].

Research issues and opportunities include:

- Biocompatibility of the implanted devices.
- Implantable power sources – battery, wireless, scavenging.
- Devices with low power, low heat dissipation and high sensitivity.
- Technologies for the development of new generations of synthetic polymers that can change their molecular conformation in response to changes in external stimuli (mechanical, temperature, pH, etc.).
- The use of low-cost technologies such as injection molding or low-cost substrates such as PDMS (polydimethylsiloxane) or polyimide for the fabrication of microfluidic devices.
- Sensor technology for the assessment of the interface activity and the progress of implant integration and functional state.
- Development of effective, long-lived, implanted systems incorporating transplanted living cells for the production of needed chemicals.
- Biomimetic membranes with built-in functionality, which can mimic real cell membranes for (stem) cell attachment and/or stimulation (proliferation, differentiation).

IIIc4. Implants interacting with the Central Nervous System (CNS)

The nervous system has a poor healing capacity. Additionally, an aging population leads to more persons acquiring disabilities - such as hearing loss, stroke, and Parkinson's disease. The demand for solutions is growing [171]. The meeting report [172] "Smart Prosthetics: Exploring Assistive Devices for the Body and Mind" focused on several themes relevant to future prosthetics where it is expected that the nanoscale will be important. The potential of nanotechnology applications in neuroscience is becoming accepted and is the subject of several reviews [69, 110, 173-175].

Dating from 1972, about 100,000 patients worldwide have received cochlear implants. The current state of this technology is bulky, difficult for the surgeon to implant and doesn't allow a broad range of perceived frequencies [176]. The human auditory nerve contains ~30,000 axons, which cochlear implants stimulate currently with 3-22 electrodes. MEMS, micromechanical devices are being developed to ameliorate these problems. Since the human ear itself already uses nanostructures [177], continued miniaturization beyond the microscale is certain to provide additional improvements.

In contrast to the auditory nerve, the optic nerve has about a million fibers. Visual prosthesis must also deal with two dimensional spatial data and the highly complex signal processing that occurs in the retina before transmission to the brain. A fully implantable retinal prosthesis would ideally capture all of the functions performed by the mammalian retina in one autonomous device. It is postulated that the needed computations can be performed at an energy efficient and physical scale comparable to biology by incorporating principles derived from neural circuits into nanoelectronic circuits [178-180].

For the control of artificial limbs the next generation of prosthetics will use regions of undamaged nervous tissue to provide command/sensory signals [181]. However, problems range from improper neuronal adhesion to inadequate signal stability. Implanted electrodes do not remain statically placed due to different flexibilities in implants materials versus tissue, or the growth of fibrous tissue around the implant. So new materials solutions are needed [182, 183]. Single wall carbon nanotubes (SWCNT) have received promising attention because of their unique physical and chemical features [184, 185]. Nanostructured porous silica is found to be more biocompatible than a smooth surface, producing less glial activation and allowing more neurons to remain close to the device [186]. Light-activated semiconducting nanoparticles have been shown to wirelessly stimulate neurons in the rat brain [187].

Research issues and opportunities include:

- Fundamental studies to find highly stable substrate and electrode materials, reliable and robust assembly, and encapsulation materials to deliver vision implants with lifetimes, biocompatibility and functionalities that are comparable to cardiac pacemakers and cochlear implants [188].
- Improving how the implanted device responds to stimuli in its local mechanical environment.
- Improving the transfer of information between the brain and/or nervous system and the device.

IIId. Biological Systems Engineering

A goal of systems biology is to fundamentally transform the practice of medicine [189-193]. Systems biology is the study of an organism, viewed as an integrated and interacting network of genes, proteins and biochemical reactions. The study of systems biology has been aided by cyber-enabled information storage/processing, advances in nanotechnology, advances in modeling and simulation, and the infusion of science and scientists from other disciplines, e.g. computer scientists, mathematicians, physicists, and engineers.

Enabled in part by the rapid progress in nanoscale science and engineering, and the growing sophistication of computers and cyberinfrastructure, systems biology is a field coming of age. The potential impact on medicine and health is enormous. Nanoscience can accelerate this field in a number of ways. First, it provides the ability to examine the properties of individual nanostructures rather than the average properties measured by techniques that require ensembles for adequate signal to noise. Work at the nanoscale enables the study of single molecule properties previously very hard to measure, such as protein folding/unfolding [194, 195], molecular motors [194], and DNA/RNA sequencing [196-199]. Second, as microfluidics and sensing technologies become further miniaturized, there will be growing capability to provide arrays that can potentially detect and identify many constituents in a biological sample in time frames of minutes rather than hours or days. Two microfluidic foundries are now available for the academic community [200]. Third, somewhat incidental but still important, the advent of nanoelectronics is continuing the increase in computational power that will be essential to model a system as complex as a cell.

The complexity of biological systems will continue to require the sampling of multiple cells. However, as with single molecule studies, the capability to probe individual cell

behavior is essential to rapid progress. Microfluidics offers analytical devices with length scales that are: a) comparable to the intrinsic dimensions of prokaryotic and eukaryotic cells, organelles and, b) the length scale of diffusion of oxygen and carbon dioxide in tissues [108, 200, 201]. The growing availability and sophistication of microfluidic chips will accelerate single cell studies [202-204]. As examples of new capabilities, nano-enabled probes have been shown to physically penetrate the cell membrane with minimal disruption [205], improve the resolution of optical probes with 3D resolution at the nanoscale [206], acquire spectroscopic [73] and fluorescent signatures [72, 207], actuate membrane receptor mediated signal transduction [208], probe cell mechanical behaviors [98, 209, 210], characterize calcium release [211], grow and probe neurons [212, 213], and probe single cell motility and metabolic calorimetry [214].

In addition to the controlled study of single cells previously mentioned, microfluidics is being utilized to study processes such as blood clotting [215]. Scaling (thousands of identical microfluidic structures) is of increasing importance in biology as the field moves toward quantitative data because it allows multiple parallel experiments under identical conditions [202].

Research issues and opportunities include:

- Microfluidic structures utilizing biocompatible materials.
- Improvements in pumping and valving.
- Improvements in on-chip sensitivity (excitation/detection) to permit single molecule detection in biological media, including inside a cell.
- Detailed understanding of single macromolecular folding/unfolding events and the role of chaperone molecules.
- Technologies that include electronic and/or communication components in forms of nanowires and nanopores for the stimulation and biosensing of cells.

IIIe. Innovations in Medical Instrumentation and Devices

Work at the nanoscale requires the continued miniaturization of measurement devices, both for spatial localization and for augmented sensitivity to the small signals associated with a nanostructure. Adaptations of these new devices for medical applications are forthcoming. As examples, the force microscope is capable of measuring differences between cancer and normal cells [98] and bone viability [216, 217]. Carbon nanotubes (CNTs) function better than glass pipettes for cellular delivery [218]. The incorporation of micro-nano-devices into catheters and other instruments is growing [219], including incorporation of Ag nanoparticles to impart antimicrobial activity [220]. Nanostructures are enabling electronic circuitry on flexible substrates, including high performance circuit elements (e.g., Si or CNT devices) [221, 222]. One can envision the incorporation of signal processing and sensing capabilities into mechanically flexible implants and even surgical gloves that might detect important parameters [75]. Nanopore-based devices show considerable promise for low cost, rapid DNA sequencing [223].

IV. Present Federal Programs

There are several U.S. Federal agencies that fund pertinent health research. The foremost is the National Institutes of Health. In addition, NASA is interested in medical practice in space; DOD has an interest in warfighter health issues and battlefield medicine; NSF provides the foundations of medicine in systems biology; EPA is concerned with impact on living systems in the environment; and USDA is concerned with impact on agriculture. The total Federal investment in the National Nanotechnology Initiative is given in Table 1. Table 3 provides an estimate of the investment more directly relevant to medicine and health.

Table 3		
Approximate Federal Investment in Nano-Science/Engn Relevant to Medicine/Health		
Agency		FY08
NIH		
	NCI - Alliance for Nanotechnology (largely centers)	30M
	NHLBI – Centers of Excellence in Nanotechnology	10M
	Nanomedicine Centers	10M
	Other	140M
NSF	Chemical, Biological, Environmental, and Transport Systems Div	25M
	Biological Sciences Directorate	25M
DOD	Mostly Multidisciplinary Univ. Research Initiative (MURI) efforts	5M

IVa National Institutes of Health (NIH)

There is an individual investigator-initiated research investment in nano-enabled medicine of about $140M/yr distributed throughout the NIH; an additional $50M is invested in centers. The NIH investment in nano-enabled medicine is monitored by a Trans-NIH Task Force.

Nanomedicine Initiative

The NIH has a Nanomedicine Implementation Group with membership from the various institutes [6]. Under its Roadmap for Medical Research – New Pathways to Discovery, NIH has established a national network of eight Nanomedicine Development Centers (NDC, see Table 4), which serve as the intellectual and technological centerpiece of the Nanomedicine initiative. These collaborative centers are staffed by multidisciplinary research teams comprising biologists, physicians, mathematicians, engineers and computer scientists. In the initial phase of the program (FY2005-FY2010), research has been primarily directed toward gathering extensive information about the chemical and physical properties of nanoscale biological structures. A second phase for the program has been approved during which the acquired fundamental knowledge and developed tools will be applied to understanding and treating disease. The Centers reach out to clinical investigators with ongoing opportunities for potential medical applications that build on the science emerging from the NDC.

National Institute of Biomedical Imaging and Bioenginering (NIBIB)
Unlike any other NIH Institute or Center, the National Institute of Biomedical Imaging and Bioengineering's mission is focused on emerging technology development. The Institute has a mandate to enable and promote fundamental discoveries, and to support the design, development, translation, and assessment of technological capabilities in biomedical imaging and bioengineering. NIBIB has programs in Micro/Nano systems [224] and Nanotechnology [225]. In addition, NIBIB sponsors Centers that are pertinent to nanotechnology. The pertinent Biotechnology Resource Centers include the Biomicroelectromechanical Systems (BioMEMS, Mass General Hospital), Biophysical Imaging Opto-Electronics (Cornell), National ESCA and Surface Analysis Center (Univ. Wash), Tissue Engineering (Tufts Univ.), and Computer Integrated System for Microscopy and Manipulation (Univ. North Carolina). The pertinent Point-of-Care (POC) Technologies Research Network includes centers on Emerging Neurotechnologies (Univ. Cincinnati), Rapid Multipathogen Detection (UC Davis), Diagnostics for Global Health (PATH, Seattle), and Sexually Transmitted Diseases (Johns Hopkins Univ.). These centers coordinate development, clinical evaluation, and reduction to practice of new POC devices. NIBIB sponsors an Interfaces Initiative for Interdisciplinary Graduate Research Training (T32) program with $3-4M/yr devoted to nanotechnology, and works with NSF and Howard Hughes Medical to address interdisciplinary training.

National Cancer Institute (NCI)
Initiated in 2004, the NCI Alliance for Nanotechnology in Cancer encompasses four major program components: Centers for Cancer Nanotechnology Excellence (CCNE, see Table 4), the Nanotechnology Characterization Laboratory (NCL, in collaboration with FDA and NIST), the Cancer Nanotechnology Platform Partnerships (CNPP, see Table 4), and a multidisciplinary research training and team development program. The funding level for the Alliance is projected at $144M over five years [226]. The partnerships are designed to develop technologies for new products in six key partnership areas: molecular imaging and early detection, *in vivo* imaging, reporters of efficacy (e.g., real-time assessments of treatment), multifunctional therapeutics, prevention and control, and research enablers (opening new pathways for research). NCI and NSF are collaborating in training programs for U.S. science and engineering doctoral students through the Integrative Graduate Education and Research Traineeship Program (IGERT) – Rutgers (nanopharmaceutical), Northeastern (brain-machine), University of New Mexico (micro-nano-bio interfaces) and University of Washington (nanotechnology workforce).

National Heart, Lung and Blood Institute (NHLBI)
Starting in 2004, the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH) has made four 5-year awards to initiate a unique, diverse, and nationwide Program of Excellence in Nanotechnology [227] (PEN, see Table 4). This program brings together bioengineers, materials scientists, biologists, and physicians who work in interdisciplinary teams to spur the development of novel technologies to diagnose and treat heart, lung, and blood diseases.

Table 4

Federal Multidisciplinary Center Programs Relevant to Medicine/Health

Program	PI Name	Institution Name	Center Title
NIH			
CCNE	Rudolph Juliano	Univ. of North Carolina	Carolina Center of Cancer Nanotechnology Excellence
CCNE	Sanjiv Gambhir	Stanford Univ.	Ctr for Cancer Nanotechnology Excellence Focused on Therapy Response
CCNE	Robert Langer	MIT	Center of Cancer Nanotechnology Excellence
CCNE	Sadik Esener	UC, San Diego	Ctr of Nanotechnology for Treatment, Understanding, & Monitoring of Cancer
CCNE	Shuming Nie	Georgia Inst of Technol.	Nanotechnology Center for Personalized and Predictive Oncology
CCNE	Chad Mirkin	Northwestern University	Nanomaterials for Cancer Diagnostics and Therapeutics
CCNE	James Heath	California Inst of Technol.	Nanosystems Biology Cancer Center (NSBCC)
CCNE	Samuel Wickline	Washington Univ.	The Siteman Center of Cancer Nanotechnology Excellence
CNPP	Douglas Hanahan	UC, San Francisco	Detecting Cancer Early with Targeted Nano-probes for Vascular Signatures
CNPP	James Baker	Univ. Michigan	DNA-Linked Dendrimer NP Systems for Cancer Diagnosis & Treatment
CNPP	Kattesh Katti	Univ. of Missouri	Hybrid nanoparticles in Imaging and Therapy of Prostate Cancer
CNPP	Scott Manalis	MIT	Integrated System for Cancer Biomarker Detection
CNPP	Panos Fatouros	VCU	Metallofullerene Nanoplatform for Imaging & Treating Infiltrative Tumor
CNPP	Paras Prasad	SUNY, Buffalo	Multifunctional Nanoparticles in Diagnosis & Therapy of Pancreatic Cancer
CNPP	Miqin Zhang	Univ. Washington	Nanotechnology Platform for Pediatric Brain Cancer Imaging and Therapy
CNPP	Jan Schnitzer	Sidney Kimmel Cancer Ctr	Nanotechnology Platform for Targeting Solid Tumors
CNPP	Mansoor Amiji	Northeastern Univ.	Nanotherapeutic Strategy for Multidrug Resistant Tumors
CNPP	Chun Li	UT Anderson Cancer Ctr	Near-infrared Fluorescence NP for Targeted Optical Imaging
CNPP	Ravindra Pandey	Roswell Cancer Inst.	Cancer Nanotechnology Platforms for Photodynamic Therapy & Imaging
CNPP	Tayyaba Hasan	Mass General Hospital	Photodestruction of Ovarian Cancer: EfbB3 Targeted Aptamer-NP
PEN	Karen Wooley	Washington Univ.	Integrated Nanosystems for Diagnosis and Therapy
PEN	Gang Bao	Georgia Inst of Technol.	Nanotechnology: Detection & Analysis of Plaque Formation
PEN	Jeffrey Smith	Burnham Institute	Nanotherapy for Vulnerable Plaque
PEN	Ralph Weissleder	Mass General Hospital	Translational Program of Excellence in Nanotechnology
NDC	Wah Chiu	Baylor College of Med.	Center for Protein Folding Machinery
NDC	Chih-Ming Ho	UC, Los Angeles	Center of Cell Control
NDC	Wendell Lim	UC, San Francisco	Engineering Cellular Control: Synthetic Signaling and Motility Systems
NDC	Gang Bao	Georgia Inst. of Technol.	Nanomedicine Center for Nucleoprotein Machines
NDC	Michael Sheetz	Columbia Univ.	Nanotechnology Center for Mechanics in Regenerative Medicine
NDC	Eric Jakobsson	UIUC	National Center for Design of Biomimetic Nanoconductors
NDC	Ehud Isacoff	UC, Berkeley	Optical Control of Biological Function
NDC	Peixuan Guo	Univ. of Cincinnati	Phi29 DNA-Packaging Motor for Nanomedicine
NSF			
NSEC	Dawn Bonnell	Univ. Pennsylvania	Center for Molecular Function at the Nanoscale
NSEC	Vicki Colvin	Rice Univ.	Center for Biological and Environmental Nanotechnology
NSEC	Richard Siegel	RPI	Center for Directed Assembly of Nanostructures
STC	Harold Craighead	Cornell Univ.	The Nanobiotechnology Center
MRSEC	Mehmet Sarikaya	Univ. of Washington	Genetically Engineered Materials Science and Engineering Center
DOD			
MURI	Jimmie Xu	Brown Univ.	Direct Nanoscale Conversion of Biomolecular Signals
MURI	G. Oberdorster	Univ. of Rochester	Physicochemical Characterization & Toxicology for Air/Space
MURI	Naomi Halas	Rice Univ.	Nanoscale Optical Imaging with Integrated Spectroscopies
MURI	H. Abarbanel	UCSD	Chem. Discrimination & Localization Using Bio-Based Olfactory Processing
MURI	Chad Mirkin	Northwestern Univ.	Bioinspired Supramolecular Enzymatic Systems

National Institute of Environmental Health Sciences (NIEHS) / National Toxicology Program (NTP)
The National Institute of Environmental Health Sciences administers the National Toxicology Program which has research activities focusing on 4 classes of nanostructured materials [228]:

- Metal oxides: the initial focus is on nanoscale titanium dioxide and zinc oxide due to their presence in cosmetics.
- Fluorescent crystalline semiconductors (quantum dots): the initial focus is on cadmium selenide/zinc sulfide spheres and rods of varying sizes and surface chemistry as a model system.
- Fullerenes: the initial focus is on carbon based fullerenes of varying cage size and surface derivatisation.
- Nanotubes: the initial focus is on single walled carbon nanotubes. Through a NIEHS-NIOSH (National Institute for Occupational Safety and Health) interagency agreement the NTP is supporting the development of exposure systems for inhalation toxicity studies of single walled nanotubes.

National Institute of General Medical Sciences (NIGMS)
The National Institute of General Medical Sciences (NIGMS) has research on, and development of, new and improved instruments, methods and technologies for nanoscience, and for the analysis of single protein and nucleic acid molecules and their complexes both *in vivo* and *in vitro.*

National Center for Research Resources (NCRR)
The National Center for Research Resources (NCRR) consortium is to transform how clinical and translational research is conducted, ultimately enabling researchers to provide new treatments more efficiently and quickly to patients [229]. Clinical and Translational Science Awards (CTSA) support clinical and translational research by providing access to clinical and translational research resources developed by the CTSAs, government sponsored research communities, government agencies or private sector. The NCRR consortium could become a powerful tool in the translation on nano-science/engineering discoveries.

NanoHealth Enterprise, public private partnerships
NIH is exploring the NanoHealth Enterprise which would comprise an integrated, interdisciplinary program that draws upon the expertise and interests of the NIH institutes and centers, in partnership with private industry, to address critical research needs for the safe development of nanoscale materials and devices. This initiative outlines an integrated, interdisciplinary program that draws upon the expertise and interests of the NIH institutes and centers, and addresses critical research needs for the safe development of nanoscale materials and devices. The initiative proposes five components: Materials Science Research, Basic Biology Research, Pathobiology Research, Informatics, and Training.

Small Business Innovative Research (SBIR) / Small Business Technology Transfer Research (STTR)
NIH is one of several agencies that have a "nano" specific topic in its SBIR/STTR announcement. Few small businesses possess the highly specialized resources needed for nanoengineering, so applications are encouraged from teams of investigators from commercial,

academic and other sectors of the research community. The NIH Pipeline to Partnerships is a virtual space for NIH SBIR/STTR awardees to showcase technology and product development for an audience of potential strategic partners and investors.

IVb. National Science Foundation (NSF)

While much of the extensive (~$350M) NSF investment in "nano" has the potential to impact medicine and health, the most directly involved programs are located in the Biological Sciences Directorate and in the Chemical, Biological, Environmental and Transport Systems Division of the Engineering Directorate. Biological Sciences has the role to promote and advance scientific progress in biology. The Chemical, Bioengineering, Environmental and Transport Systems Division (CBET) supports research in bioengineering (among other topics). These two programs provide much of the underlying science and engineering base for medicine and health applications, which is critical to rapid advancement.

The CBET Division has programs in "Integration of Life Sciences with Engineering", as well as "Nanoscale Science and Engineering." The current high-emphasis research and education areas include: post-genomic engineering, tissue engineering, biophotonics, and nano-biosystems. CBET has approximately $25M invested in nano-bio projects.

The Molecular and Cellular Biosciences (MCB) Division effort under the Biological Sciences Directorate at NSF emphasizes systems biology; it has approximately $25M invested in nano-bio projects. The research includes databases and informatics, instrument development, biomolecular systems, cellular systems, and genes and genome systems. The latter three encourage multi-disciplinary approaches, including research carried out at the interfaces of biology, physics, chemistry, mathematics and computer science, and engineering.

The National Nanotechnology Infrastructure Network (NNIN) is an integrated partnership of thirteen user facilities, supported by NSF, providing unparalleled opportunities for nanoscience and nanotechnology research [230]. The network provides extensive support in nanoscale fabrication, synthesis, characterization, modeling, design, computation and hands-on training in an open, hands-on environment, available to all qualified users.

IVc. Food and Drug Administration (FDA)

The regulation of nano-enabled products may involve more than one traditional FDA category, for example a "drug" delivery "device". In these cases the assignment of regulatory lead is the responsibility of the Office of Combination Products. To facilitate the regulation of nanotechnology products, the Agency has formed a NanoTechnology Interest Group (NTIG), comprised of representatives from all its Centers. The NTIG meets quarterly to ensure there is effective communication between the Centers. A FDA task force report on nanotechnology is available [21]. The FDA is a cosponsor of the Nanotechnology Characterization Laboratory, along the NCI and NIST, and the nanostructure evaluation in the National Toxicology Program with NIEHS. There is a FDA intramural research program, but it does not presently have any "nano" focused projects.

The FDA and Alliance for NanoHealth co-convened a workshop on nanomedical regulatory science in Houston in March 2008 to identify the top scientific hurdles in bringing

nanoengineered products to patients, specifically in the pre-clinical, clinical and manufacturing phases of product development [231]. Six priority areas were identified:

- Determination of the distribution of nanoparticulate carriers in the body following systemic administration through any route.
- Development of imaging modalities for visualizing the biodistribution over time.
- Understanding mass transport across compartmental boundaries in the body.
- Develop new mathematical and computer models that will lead to predicting risk and benefit parameters.
- Establish standards or reference materials and consensus testing protocols that can provide benchmarks for the development of novel classes of materials.
- Realization of an analytical toolkit for nanopharmaceutical manufacturing, accompanied by specification sheet of toxicological, safety, and biodistribution properties obtained through standardized, validated methods.

IVd. Department of Defense (DOD)

The DOD does not have any appreciable program in nanomedicine *per se*. The DARPA Defense Science Office has thrusts on tactical and restorative biomedical technologies that may exploit nanotechnologies. There are some limited efforts from the various service research offices are examining how to exploit nanotechnology with medical implications; five such Multidisciplinary University Research Initiatives (MURIs) are listed in Table 4 and ONR has a recent initiative on Autonomous Devices for Advanced Personnel Treatment. The Army funds the Institute of Soldier Nanotechnologies (MIT University Affiliated Research Center) that addresses some medical applications. The Army Telemedicine and Advanced Technology Research Center (TATRC) oversees a diverse portfolio, largely Congressional adds to the DOD budget, ranging from new nanomaterial-based contrast agents for cardiac and brain imaging to novel drug delivery systems for the treatment of cancer. In each case TATRC assists the program in identifying military needs, defining metrics, and comparing the new technology to existing methods.

IVe. Department of Energy (DOE)

The DOE Nano Centers are user facilities for interdisciplinary research at the nanoscale. Each of the five Centers is co-located with other large scientific facilities to take advantage of complementary capabilities, such as the Spallation Neutron Source at Oak Ridge, the synchrotron light sources at Argonne, Brookhaven and Lawrence Berkeley, and semiconductor, microelectronics and combustion research facilities at Sandia and Los Alamos. The Centers contain clean rooms, laboratories for nanofabrication, one-of-a-kind signature instruments, and other instruments (such as nanopatterning tools and research-grade probe microscopes) not generally available except at major scientific user facilities.

IVf. European Union (EU)

The Framework 7 included an ERA-NET (European Research Area – network) on nanomedicine project - NMP-2008-4.0-13 - with the expectation of: improved coordination and reduced overlapping and fragmentation; achieving critical mass and ensuring better use of limited resources; sharing good practices in implementing research programs; and promoting

transnational collaborations and generate new knowledge. In FY08 approximately €8M was allocated for the first call ERA-NET plus (of which nanomedicine is a part).

As another example, the project "Healthy Aims: Developing New Medical Implants and Diagnostic Equipment" is a €23M, four year project to develop intelligent medical implants and diagnostic systems. While not constrained to nanotechnology-enabled, products under development will almost certainly benefit from nanoscale capabilities. The funded projects include: retinal implant, functional electrical stimulation of systems for restoration of upper-limb movement as well as bladder and bowel control, cochlear implant, glaucoma sensor, intracranial pressure sensor, and a sphincter sensor for monitoring bladder pressure [232].

The European Technology Platform: Nanomedicine – Nanotechnology for Health identifies the following as strategic research priorities [7]:

Diagnostic issues
- *In vitro* diagnostics.
- *In vitro* and *in vivo* imaging.

Drug/Delivery/Therapeutic Issues
- Improving targeting agents.
- Formulation and stability of pharmaceutics.
- Easier routes of administration – crossing biological barriers.
- Nanodevices for targeted delivery.
- Bioactive signaling molecules.
- Cell-based therapies.

Implant/Tissue Regeneration Issues
- Interactions between biological systems and artificial nanostructures.
- Intelligent biomaterials and smart implants.

Overarching Issues
- Basic science deficiencies.
- Medical devices.
- Moving established and novel nano-therapeutic delivery systems from the laboratory to the clinic.

V. Recommendations

Research opportunities and challenges have been identified in each of the subcategories in Section III; they are many. It should be noted that more generic questions were addressed in this workshop, and that the research funding levels and prioritization amongst these opportunities and challenges was beyond its scope. From the discussions at the Re-Engineering Basic and Clinical Research to Catalyze Translational Nanoscience Workshop at USC, augmented by literature search and subsequent evaluation by other experts, the following overarching recommendations are made:

- Medicine enabled by nanoscale science and engineering
    - The continuing progress in nanoscale science and engineering promises to create revolutionary opportunities for medicine and health; the investment in the basic discoveries should not be diminished. Rather additional funding should be found for the translational efforts.
    - The Trans-NIH Nano Task Force deserves kudos for its efforts to inject nanoscience into the NIH portfolio, but only a handful of the NIH Institutes (NCI, NHLBI, NIBIB) have created explicit programs to exploit the nanoscale. As progress at the nanoscale continues to progress, other NIH Institutes should be encouraged to develop explicit efforts to engage the nanoscience and nanoengineering communities.
    - The NIBIB website, Nanotechnology at NIH, provides a central location for the various NIH programs, is a valuable resource for the science/engineering communities, and should be kept up to date.
    - As nano-enabled improvements are incorporated into functional medical devices and systems, it will become more difficult to track the "nano" impact. NIH is encouraged to make that effort, both to better understand where nanotechnology provides viable solutions, and to document those contributions for inclusion in social and political debates.
    - Continue and expand the efforts to build bridges between the physical sciences, engineering, the medicine/health professionals, and the medical technology industries. Centers are a means to accomplish this goal, but affect only a limited number of individuals. There are several extant professional forums that address translational nanomedicine, including the BioMaterials Society, but the cross-fertilization between clinical physicians and the nanoscience research investigators is minimal. Gordon Conference-like meetings with limited attendance and a site designed to encourage full participation over a weeks span should be encouraged. It may be necessary to offer financial assistance or continuing education credits as incentives to clinicians to enable their participation. One of the more promising outcomes from the Re-Engineering Basic and Clinical Research to Catalyze Translational Nanoscience Workshop was interaction amongst the participants with the anticipation of fruitful collaborations.
    - The NIH should encourage its employees and grantees to contribute to the much needed efforts in developing standards by the American Society of Testing and Materials (ASTM), American National Standards Institute (ANSI), and International Standards Organization (ISO). The development of good standards

- The Nanotechnology Characterization Laboratory (initiated by NCI, NIST and FDA), or its equivalent(s), should be expanded for access by all nanomedicine research. Because of their relative newness and the difficulty in their analysis, nanostructures tend not to be well characterized. This can lead to erroneous interpretations of experimental work and has been a source of problems.

- Translation
  - The Clinical and Translational Science Awards (CTSA) program should explicitly encourage injection of nano-enabled technology into clinical settings. The National Center for Research Resources (NCRR) consortium is meant to transform how clinical and translational research is conducted, ultimately enabling researchers to provide new treatments more efficiently and quickly to patients. Nano-enabled medicine and health technologies will be rapidly maturing; facilitating their translation into the clinic will be highly worthwhile.
  - The Bioengineering Nanotechnology SBIR/STTR announcements provide a useful approach to translation. With due attention to return on investment, continuing these explicit SBIR/STTR announcements is encouraged.
  - There should be a translation program identified and publicized for nano-enabled medicine/health. Several NIH Institutes have a cooperative program in translational research. Those programs facilitate solicitation, development, and review of therapy-directed projects to accelerate the translation of basic research discoveries into therapeutic candidates for clinical testing. Since multidisciplinary approaches are important to nanomedicine, and many of the contributors are not familiar with NIH, the NIBIB 'Nanotechnology at NIH' website should provide explicit mention of this, or similar, opportunities.
  - The NIH should explore partnering with NSF and DOE to expand the nanoscale user facility capabilities with specific focus on nanomedicine needs. While the NNI has funded a number of User Facilities for Nanoscale fabrication/ characterization, they are not focused on medical needs. Biocompatible materials and materials processing are frequently not compatible with traditional semiconductor processing. In the UK, a joint venture has been formed between the University College of London and Imperial College BioNano Consulting to better enable industry to access the UK leading research capability in the field of bionanotechnology. It is meant to help companies with prototyping and characterization.
  - There is need for a science base to develop understanding of the critical parameters that can provide generic guidance to the FDA approval process. The FDA and Alliance for NanoHealth Workshop (see section IVc) identified six priority areas for research. Since the FDA research budget is limited, NIH (and NSF) should work with the FDA to create programs addressing those areas.
  - The Department of Commerce should work to ensure well constructed patents in the highly multidisciplinary nano-enabled biotechnology topic and to facilitate workable licensing arrangements amongst the various commercialization partners. Establish a nanomedicine group within the USPTO. Given the complexities of

- Provide mechanisms for better interfacing between industry, academia and government. Establish protocols and technology transfer policies that foster translation of nanomedicine. Some suggestions are: a) Simplify the pathway from invention to innovation/commercialization though new IP practices. The time and expense required for negotiating collaboration and licensing agreements must be reduced; b) Encourage industry participation in NIH Nanomedicine Centers, both as advisory board members and researchers; c) Encourage industrial participation on NIH peer review panels; and d) To accelerate translation, encourage industrial participation on NIH grants, both as consultants and where appropriate as researchers.
- NIH should explore mechanisms such as the DARPA programs and the NIST Technology Improvement Program whereby industry can participate in translation efforts. The pending NanoHealth Enterprise effort to promote public-private partnerships could have real value in accelerating translation (as well as ameliorating ESH concerns). However, care must be taken to fully engage the private sector rather than impose government priorities.

- Environmental / Safety / Health (ESH) Concerns
  - The NNI reauthorization legislation specifically identifies this topic for augmented investment. However, the size of any investment must be carefully examined to ensure that adequately characterized materials are utilized; otherwise improper conclusions may be drawn from a study. As noted above, the Nanotechnology Characterization Laboratory, should be either expanded to service all of the nanomedicine efforts or a sister laboratory created to serve that function.
  - There is a challenge to create and maintain databases that will be easily accessed by all. The NIH NanoHealth Enterprise is looking to develop public-private partnerships about three topics – nanobioinformatics, nanostructure characterization, and nanostructure/bio interactions – and is one possible approach to addressing this need.
  - The funds identified for ESH research in the NNI is growing. The ESH work will also be relevant and important to medicine/health. Conversely, research in medicine/health will certainly involve fate and effects of nanostructures in living systems and will be useful for ESH. Looking for harmful and beneficial effects of a nanostructure are two sides of the same coin; there is need keep the two communities working closely together.
  - ESH concerns are not unique to the U.S. The NSET agencies, and NIH in particular, must be aggressive in fostering international collaborations to take advantage of other programs.
- Systems biology
  - To address the breadth and complexity of the science and engineering challenges inherent in systems biology, a concerted national program is warranted. Given the

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