CRITICAL NATIONAL NEED IDEA

NANOMANUFACTURING: THE MISSING LINK BETWEEN DISCOVERY AND PRODUCTS

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Introduction

Richard Feynman's classic lecture in 1959, "There's Plenty of Room at the Bottom," issued several challenges that have continued to spur interest in creating and manipulating objects on a very small scale. Since that time, researchers have increasingly turned their attention to understanding and creating technology that acts at the molecular and even atomic scale. Nanotechnology is viewed throughout the world as a critical driver of future economic growth and as a means to solving some of humanity's most vexing challenges. Because of its incredibly broad range of prospective uses, nanotechnology has the potential to impact virtually every industry, from aerospace and energy to healthcare and agriculture.

Realizing this potential requires progress on many fronts of science and engineering. Ultimately, it will take reliable tools and processes for assembling the basic building blocks of nanotechnology products, cost-effectively producing these products in large quantities, and integrating them into systems spanning nanoscale to large-scale dimensions. Developing these core competencies in the United States will lead to a new, more sophisticated manufacturing sector.

In today's global environment, time is a critical factor. Manufacturing R&D must closely follow discovery to ensure that US companies can transform innovation into products. The U.S. manufacturing sector faces new opportunities as well as new challenges[i]. There is strong consensus in industry, academia, and government that the future competitiveness of U.S. manufacturing — and all that it underpins — will be determined, in large part, by research, innovation, and how quickly firms and industries can apply and incorporate new technologies into high-value-added products and high-efficiency processes. The field of nanotechnology clearly offers profound opportunity for numerous industries including the manufacturing sector itself.

Nanomedicine, an offshoot of nanotechnology, refers to highly specific medical intervention at the molecular scale for curing disease or repairing damaged tissues, such as bone, muscle, or nerves. At this size scale – about 500 nanometers or less –biological molecules and structures operate inside living cells. The application of nanotechnology in life sciences is quickly becoming a hot research topic for drug design and drug delivery. The nanotechnologies, including nanoparticles and nanodevices such as nanobiosensors and nanobiochips, are used to improve drug discovery and development. Nanoscale assays can contribute significantly to cost-saving in screening campaigns. Many drugs discovered in the past cannot be used in patients because a suitable method of drug delivery was lacking. Nanomedicine technologies have tremendous potential for *transformational results* – disruptive changes over and above current methods and strategies for heathcare, with wide-ranging implications.

Government funds for nanotechnology research have created some of the most sophisticated nanoscience laboratories in the world. Yet, research in nanotechnology to date has been largely focused on the discoveries of novel physical and chemical properties of various metallic, inorganic, or carbon-based materials, with a notable absence of capabilities and funds focused on manufacturing nanomaterials and their incorporation into products. Further, because of the historic, heavy emphasis on inorganic nanomaterials, the gap for manufacturing organic nanomaterials relevant to biotic systems is appreciably larger.

Maps to Administration Guidance

The long-term vision of scientists from a multitude of fields has been the fabrication of a wide range of materials and products with molecular-scale precision. However, experts in the field have had strong differences of opinion on how rapidly this will occur. It is uncontroversial that expanding the scope of nanoscale precision will dramatically improve high-performance technologies of all kinds, from medicine, sensors, and displays to materials and solar power.

Specifically for nanomedicine, the ability to manipulate size, shape, chemistry and modulus of nanomaterials can have wide-ranging impact on how we diagnose and treat disease. New abilities to tune these features can provide researchers with a more thorough understanding of "how" and "why" cellular and organ systems react, allowing scientists to build highly efficient tools that can safely operate inside the body. New technologies that have the power to control size, shape, and other functionalities are currently being developed and have shown remarkable promise, but significant investment in *scaling-up* and producing engineered nano-structures in a *cGMP* environment is necessary to bring innovations to commercial reality.

These new technologies are leading the charge in innovative new therapeutics and devices for the leading causes of death (e.g. cancer and cardiovascular disease), disease prevention (e.g. vaccines), and enabling whole new classes of therapeutics (e.g. oligonucleotides):

- **Cancer** accounted for around 12% of deaths worldwide, and more than 10 million new cases of cancer emerge each year. In many countries, more than a quarter of deaths are attributable to cancer. The integration of nanotechnology within cancer research promises to increase our understanding of how cancer progresses; the identification of biomarkers will help predict disease susceptibility and precancerous lesions, while multifunctional nanoscale devices could potentially simultaneously detect and treat cancer.[ii]
- **Cardiovascular disease** (CVD) is the leading cause of death in the world, killing almost 17 million people each year and is a tremendous financial burden on the healthcare system estimated to cost the US around $560 billion annually.. The application of nanotechnology in diagnosis, imaging and tissue engineering will have a vital role to play in determining the underlying mechanism of various CV systems such as atherogenesis, and the future development of novel therapeutics, medical devices and regenerative tissues.
- **Vaccines** are responsible for the control of many infectious diseases that were once common in this country, including polio, measles, diphtheria, whooping cough, rubella (German measles), mumps, and tetanus. With very few adjuvants currently being used in marketed human vaccines, a critical need exists for novel immunopotentiators and delivery vehicles capable of eliciting humoral, cellular and mucosal immunity. Such crucial vaccine components could facilitate the development of novel vaccines for viral and parasitic infections, such as hepatitis, HIV, malaria, cancer, etc.[iii]
- In the ten years that have passed since Andrew Fire, Craig Mello, and colleagues discovered the ability of double-stranded **RNA to silence gene expression** in worms, billions of dollars have been invested in therapeutic applications of gene silencing in humans. Several products are in the clinic for the treatment of age-related macular degeneration and other diseases where localized delivery to the eye or lung is possible. However, to enable the widespread use of siRNA in the clinic, safe and effective delivery approaches are needed to enable systemic delivery. Nanotechnology platforms hold the key to enabling this promising class of compounds.

In the U.S., the National Nanotechnology Initiative (NNI) has been instrumental in focusing world attention on nanoscience and has provided world leadership in establishing the necessary interdisciplinary research. A major opportunity exists to leverage the past eight years of NNI research platforms and to establish programs to translate this knowledge into viable products through the advancement of atomically precise technologies. Our aim in this white paper is to call for the commercial development of Nanomanufacturing Technologies that will address the grand challenges of health care and other fields that will benefit from such infrastructure. Manufacturing R&D must go hand-in-hand with scientific discovery to ensure that U.S. manufacturers can quickly transform innovations into processes and products.

Delivering the many anticipated nanotechnology products of the future will require entirely new scalable manufacturing processes. These include cost-effective and quantity-relevant methods for synthesizing and processing particles, tubes, fibers, and quantum dots; positioning, imaging, and measurement at nanoscale resolution; and modeling of manufacturing processes from nanoscale to macroscale. Several of these manufacturing processes are currently being realized in diverse but restricted scale forms, and they will need to be refined continuously to fully realize the promise of future nanotechnology products. The challenge is to build on these achievements and expand them to produce a wider range of structures, providing systems of larger scale, greater complexity, and increasingly higher performance. Key challenges in nanomaterial manufacturing processes are summarized below.

1. Scale-up of manufacturing processes from small lot sizes to mass production poses the first key challenge for manufacturing nano-scale products and materials. Process engineers need approaches that use mass production techniques and integrated assembly to reduce costs and accelerate the entry of nanomaterials into commercial applications. Unit operations that comprise these production methods must be scaled successfully and reproducibly from laboratory processes into production rates, while preserving the inherent nanoscale properties in the finished materials. While chemical processes typically deal with a immense number of structures with relatively simple assembly processes, and electronic processes typically deal with a much smaller number of structures but highly complex assembly processes, nanomanufacturing will be called upon to deal with both a large number of structures and a highly complex hierarchical assembly, requiring major innovations.

2. Integrating bottom-up and top-down nanoscale processes into new manufacturing paradigms is the second key challenge. Today's first-generation nanoproducts are frequently manufactured with traditional manufacturing techniques, which can be prohibitively expensive and/or have limited throughput for many applications. For example, using photolithographic or direct-write methods to produce isolated particles on a "10's of wafers per hour" level would result in milligram quantities of product per day. Even highly touted tip-based nanomanufacturing processes has an inherently low rate of production in terms of mass throughput, producing 1×10^{-21} grams of product per batch in 2007.[iv] Current macroscopic assembly processes such as crystallization and mixing do not readily lend themselves to the fabrication of hierarchical systems of nanostructures.

3. Advanced analytical tools for probing and metrology that extend beyond optical resolution pose the third challenge to manufacturing processes. Nanomanufacturing processes must have effective control systems with accurate, timely measurements and rapid data assessment and response parameters. Advancements in high-volume, cost-effective production depend on the development of next-generation instrumentation for accurate and rapid characterization of nanomaterials. Optical methods currently used in metrology can be accurate, fast, and

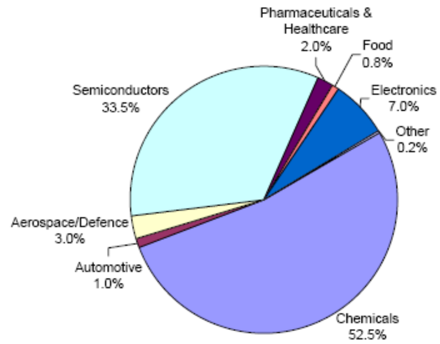
integrated in-line for process control, but have reached their detection and resolution limits for probing nanoscale structures. Integrating the process control components at the nanoscale will require a long-term commitment to R&D in diverse science and technology fields.

Existing Efforts. Research activities in nanotechnology are an international effort. The U.S. has adopted a multidisciplinary approach and passed a bill in 2003, the NANO ACT, to encourage the "creation of partnerships, raise awareness, and implement strategic policies to resolve obstacles and promote nanotechnology." This bill authorized funds worth $4.7B over five years, beginning in 2004. However, this budget was cut to $3.7B over four years from 2005. A related bill was introduced in February of this year. One relevant section directs the Secretary of Commerce, if $100 million is made available from the private sector for establishing a Nanomanufacturing Investment Partnership, to establish such a Partnership to provide funding for precommercial nanomanufacturing research and development projects.[v]

In the US alone, there are currently more than 50 institutes and centers dedicated to nanotechnology R&D, as well as focused efforts within multiple agencies. The table on the right summarizes the nanomanufacturing R&D efforts by agency and application area.[vi] While there are multiple opportunities to investigate basic research on materials synthesis and characterization, including nanocomposites, atomic-layer deposition for nanoelectronics patterning, templating polymeric and biomolecular systems, directed assembly of 2D and 3D structures and modeling/simulation, there are few opportunities to translate these processes to commercial production.

IWG Agency	Infrastructural Applications	Product/Process-Specific Applications
DHHS	• Environmental safety and health • Physical characterization and in-vitro assays of nanoparticles • Informatics tools for predicting biophysical properties and interactions; promote data sharing • Workforce education and training	• Nanoscale diagnostic and therapeutic devices
DOC/NIST	• Measurements, standards, and data crucial to both private industry's development of nanotechnology-based products, as well as Federal agencies' efforts to exploit nanotechnology to further their missions, such as national security and environmental protection • Enable science and industry by providing essential measurement methods, instrumentation, and standards to support all phases of nanotechnology development, from discovery to production.	
DOD		• Nanostructures for defense devices, systems, and materials • Material surface treatment and coatings
DOE	• Basic research on nanomaterials: synthesis and characterization	• Possibility of developing technology platforms for manufacturing
EPA	• Ecological and human safety and health assessment • Life Cycle Assessment	• Nanodevices for environmental treatment, remediation, and sensing • Nanomaterials as substitutes for toxic materials • Life cycle material and energy efficiency realized through nanotechnology
NASA		• Miniaturized sensors for space exploration • Lightweight, high-performance, multifunctional structures
NSF	• Research on obstacles to high-rate production and nanomanufacturing reliability, robustness, yield, efficiency, and cost effectiveness • Workforce training and education	
USDA	• Biologically based nanoscale manufacturing of materials and devices • College-level education of nanobiotechnology relevant to agriculture and food systems	• Nanoscale detection of food pathogens and toxins • Functionalize nanoparticles for food safety intervention • Nanoscale delivery of nutraceuticals in foods

Notably absent from the table of agencies participating in nanomanufacturing R&D is NIH. Traditionally, "nano" has been dominated by materials science and analytics. This trend can easily be seen in the government-sponsored nanoscience laboratories such as the Center for Functional Nanomaterials (CFN), and the Center for Hierarchial Manufacturing at UMass Amherst. NIH does fund a network of nanotechnology research centers, supported by both individual NIH institutes and the NIH-wide Nanomedicine Roadmap Initiative. The Centers' programs promote multidisciplinary research and development that engage basic biological, physical science, clinical perspectives and expertise, rather than focus on manufacturing R&D that will lead to commercial products. This disproportion is evident in the current applications of nanotechnology, shown in the pie chart to the right.



Numerous state-wide initiatives also exist to promote awareness and investment in nanotechnology. However, these initiatives should be supplemental to an overarching strategy at the national level for nanotechnology development and manufacturing.

Based on the level of funding already given, there is no doubt that nanotechnology development is a national priority. The most recent report of the Interagency Working Group on Manufacturing R&D emphasizes that manufacturing R&D must go hand in hand with scientific discovery to ensure that US manufacturers can quickly transform innovations into products and processes. Nanomanufacturing is the means through which the Nation will realize the benefits of nanotechnology. These benefits will result through enhanced performance of products in a wide range of industries that include aerospace, automotive, communications, energy, environmental remediation, information, medical, pharmaceutical, and power. At the same time, realizing the promise of nanotechnology through the development of practical manufacturing methods will likely lead to industries and products yet to be imagined.

Justifies Government Attention

Nanotechnology research is still in its infancy, and it may be at least five years or more before the first generation of truly engineered nanoproducts and nanodevices become commercially available. The pharmaceutical industry continues to evaluate the potential of new technologies to alleviate the burden of rising research costs, improve the speed and efficiency of the discovery process, and create high-value new generation therapeutics. While nanotechnology is widely seen as having huge potential, the pharmaceutical industry remains cautious to the idea it will be the universal remedy to their problems. This may be a primary reason why companies have been slow to invest resources in this area.[vii]

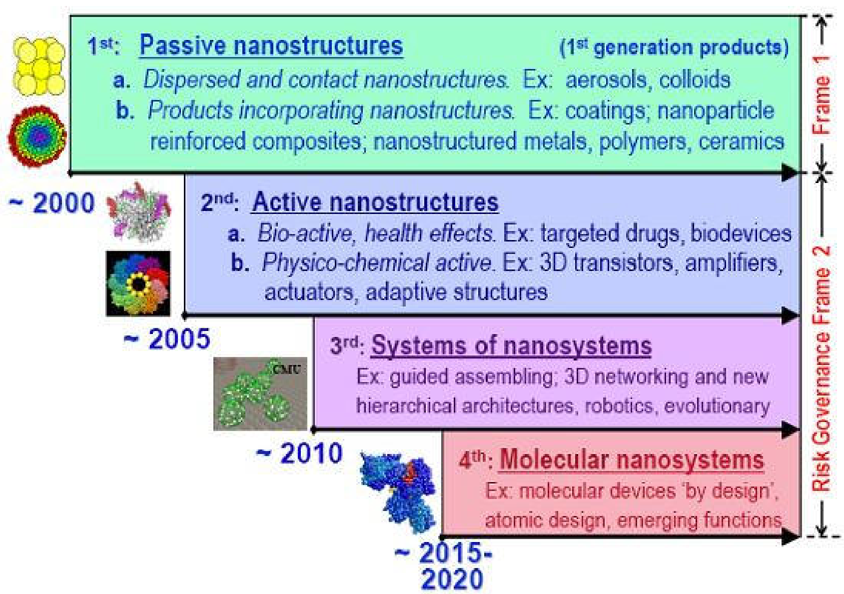
However, we believe there are number of technology innovations that are and can be driven through government funding that will stimulate the industry to re-evaluate its position:

- nano-engineered drugs can be designed to improve the therapeutic potential of approved or shelved products;
- nano-engineered drugs may improve dosing regimens, reduce drug dosage and potentially reduce the cost of treatment in the longer-term;
- nano-engineered drugs may open up new opportunities to target disease;
- nano-enabled delivery systems have the potential to deliver approved and new products in a targeted manner and thus reduce off-target effects;
- nano-enabled delivery systems have the potential to deliver a wide-range of “difficult-to-deliver” products such as large macromolecules (e.g. peptides & proteins) or toxic small molecules (e.g. chemotherapy agents);
- new nanomaterials may have potential applications in medical devices and implants;
- nanomaterials and nanosensors have potential applications in medical imaging, diagnostics and point-of-care helping to detect disease earlier

However, private investment in this technology must be weighed against the risks of this relatively new field where considerable investment has already taken place in academia, which has yet to fully validate and deliver cost-effective and commercially viable platforms. Government funding in Nanomanufacturing R&D is needed to realize the investments that have already been made. Bridging the gap from proof-of-concept to commercial viability will provide the risk mitigation needed to encourage the private sector to support and further develop nanomedicine platforms.

The potential for disruptive change in the heathcare sector through the use of nanotechnology is becoming increasingly evident. With these next-generation therapeutic and diagnostic agents, we can radically improve our understanding of biological systems. Leading researchers in the nanotechnology field, such as Mihail Roco of the US National Nanotechnology Initiative, believe the field of nanotechnology will evolve through stages from relatively simplistic nanostructure/nanomaterials for specific uses to complex functional nanosystems. These four generations of nanotechnology development (see chart below)[viii] go from passive structures designed to do single simple tasks, through a second generation of multicomponent structures, to complete systems in the years to come.

Nanotechnology research spans from the large pharmaceutical companies such as AstraZeneca, GlaxoSmithKline, Novartis, Roche and Pfizer, to specialty pharma companies like Elan and Genentech, and nanotechnology start ups such as Abraxis Biosciences, pSivida and StarPharma, in addition to the profusion of academic work. Translational funding would be welcomed by small and large enterprises, particularly those focused in the areas of drug delivery and diagnostics. For example, companies focused on nanoparticle-based delivery that could commit to a program include Abraxis, AlphaRx, Calando, Eurand, Liquidia, NanoBioMagnetics, Nanohorizons, Nanosphere, and Protiva, to name a few. These companies would likely propose individual efforts, or partner with a larger pharmaceutical group to bring new technology into the clinic. In addition to nanoparticle technologies, there are a host of other bottom-up and top-down nano-platforms that would benefit from translational resources, including nanorod, nanocrystal, self-assembly, and tip-based approaches.

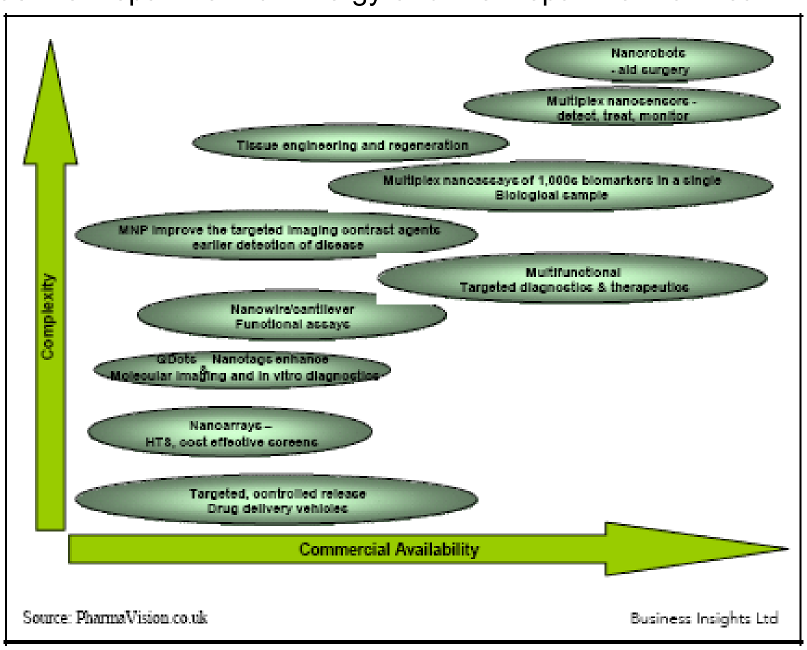


Essentials for TIP funding

The challenge for funding in this field will be to build programs with the right participants and incentives to take nanotechnologies from early demonstrations to scalable systems, products, and industries. A program under university control could, and has fostered research, but there is no direct support for development. Government lab controlled program could make the first steps towards development, but would not bring technologies and products to market. Industry involvement is essential for program focus and rapid deployment of the technologies developed; however, companies have limited ability to invest in long-term research. Large public companies shy away from significant, risky R&D expenditures, and small private companies lack the necessary resources.

Targeted, government-driven funding can make a crucial difference in the scale, breadth, and time horizon of industry-driven R&D for Nanomanufacturing. In the US, the largest funding opportunities that seed commercialization activity are the Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs. These programs are extremely limited in the terms of time and budget needed to support innovation in technology infrastructure. Transitioning a prototype process to a viable commercial scale is an effort that requires capital expenditure and timelines well beyond that of the SBIR and STTR programs, which in most cases offer a $100K phase I effort for a 6-month to 1 year effort. In addition, many nanomedicine-based businesses are venture backed, requiring significant capital for pre-clinical studies prior to revenue. These companies are often not eligible for SBIR and STTR programs due to ownership requirements.

The TIP program uniquely has the opportunity to bridge the gap between the research lab and the market place. As one of the only programs that offers meaningful routes of funding to the private companies, these projects facilitate the development of core technology necessary for success as well as generates the risky, early stage data needed to engage other funding sources, including both government and the private sector. This early funding enables the generation of the level of technology and relevant data necessary for feeding the pipeline for other government programs, such as the Department of Energy and the Department of Health and Human Services. TIP serves a crucial role as a feeder for these more mission-oriented programs



Without additional funding, nanotechnology platforms will likely continue to grow, due to their tremendous potential as described earlier. But researchers have only begun to scratch the surface of this potential, and nanotechnology platforms will unlock many more doors to come if engineers and scientists can develop and improve processes for manufacturing engineered nano-structures in a cost-effective manner. The figure on the previous page gives a sense for the future impact that nanotechnology will incur in the healthcare space alone. However, nanotechnology will not change things overnight. Without focused resources, it may take several decades to sharpen the technology to the stage at which commercial nanodevices are available to monitor disease progress and administer therapeutics accordingly. Pharmaceutical companies have generally taken a "watch and see approach", and relatively few have established dedicated laboratories to explore the capabilities of nanotechnology in the market. Instead, companies continue to evaluate the potential of this technology through alliances with academic researchers and leading institutes, without addressing the "800 pound gorilla" of manufacturing scale-up.

For the U.S., time is a critical factor in ensuring that our investment in nanotechnology innovation can be transformed into commercial products. Manufacturing R&D must closely follow discovery to ensure that US companies can compete in this high-value market, and government support is needed to guarantee development of the infrastructure to support the grand challenges of health care, energy, and other fields that will benefit from such development. The era of nanotechnology is upon us. The only question remaining is how quickly and widely the US will establish these new manufacturing paradigms. Will the country "wait and see" how the industry develops, entering the global marketplace at a later and more costly stage; or will the U.S. make the necessary investments to advance nano-manufacturing processes for products that will improve the health and lives of future generations?

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[i] 2004 Commerce Department report, Manufacturing in America

[ii] Barton, C.L. "Nanotechnology: Revolutionizing R&D to develop smarter therapeutics and diagnostics" Business Insights, Ltd. 2007.

[iii] Peek LJ, Middaugh CR, Berkland C."Nanotechnology in vaccine delivery" Adv Drug Deliv Rev. 2008 May 22;60(8):915-28.

[iv] "Productive Nanosysems: A Technology Roadmap" 2007 Battelle Memorial Institute and Foresight Nanotech Institute, authored by UT-Battelle, LLC under contracts from the Department of Energy.

[v] The Library of Congress, Summary of H.R.820

[vi] Manufacturing the Future: Federal Priorities for Manufacturing Research and Development, Report of the Interagency Working Group on Manufacturing R&D, Committee on Technology, National Science and Technology Counsel, March 2008.

[vii] Lux Research, The Nanotech Report Investment Overview and Market Research for Nanotechnology, 3rd Edition, 2005

[viii] Center for Responsible Nanotechnology, http://www.crnano.org/