PROGRESS AND PLANS OF NATIONAL NANOTECHNOLOGY INITIATIVE (NNI) AGENCIES

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Summary

NIH advances creative, fundamental discoveries and translational nanotechnology research and development to ultimately enhance health, lengthen life, and reduce illness and disability through a variety of mechanisms and approaches. The NIH nanotechnology investment portfolio encompasses both basic and clinical research funded primarily through grants. Current research efforts focus (and will continue to focus) on advancing new medical diagnostics and therapeutics; supporting nanotechnology-related environmental, health, and safety (EHS) research; developing nanotechnology information resources; and training a new generation of nanotechnology researchers. Due to the successful integration of nanotechnology-based R&D into broad areas of biomedical applications, scientists can propose ideas via non-nanotechnology-specific research opportunity announcements that are supported by a large number of NIH institutes.

Select research areas of increasing or continued interests to specific NIH institutes include the following:

- **Vaccine Development:** The National Institute of Allergy and Infectious Diseases (NIAID) Vaccine Translational Research Branch (VTRB) will be funding the Integrated Preclinical/Clinical AIDS Vaccine Development Program (IPCAVD) through fiscal year (FY) 2018. The IPCAVD program is designed to enable a multidisciplinary team of investigators to complete all steps necessary from down-selection of a vaccine candidate through Current Good Manufacturing Practice (CGMP) manufacture/testing/product release and into clinical trials. VTRB is also managing the regulatory and Investigational New Drug (IND) filing for membrane-proximal external region (MPER) peptide-liposome nanoparticles for use in a first-in-man phase I clinical trial to evaluate safety and immunogenicity. MPER from gp41 is a promising antigen segment of the viral envelope recognized by a number of broadly neutralizing antibodies. The virion lipid is an important component of the binding immunogen for the gp41 MPER neutralizing epitope, and represents a promising vaccine target.

- **Tissue Regeneration and Repair:** The National Institute of Dental and Craniofacial Research (NIDCR) has made several strategic investments in nanotechnology-based initiatives to improve dental, oral, and craniofacial (DOC) health. NIDCR leverages its investments on the significant promise of nanotechnology as an invaluable tool to produce novel structures that induce regeneration and repair of biological tissues, deliver biomolecules to tissues with pre-defined kinetics, and control tissue infection and inflammation, among other uses. Additional areas of nanotechnology research focus on biosensor technologies for detection and monitoring of complex biological events within the oral cavity to aid in diagnosis, treatment, and management of DOC and systemic diseases.
• **Cancer Research:** The National Cancer Institute (NCI) supports research strategies using nanotechnology to explore cancer biology and resolve clinical problems in oncology. For instance, the NCI Alliance for Nanotechnology in Cancer program has evolved from conducting preclinical studies to evaluating experimental drugs and imaging agents in clinical trials. NCI also funds many grants that utilize nanotechnology to advance outcomes in clinical oncology through various other programs within the Division of Cancer Treatment and Diagnosis.\(^1\) Examples include research on targeted near-infrared agents to improve image-guided surgery, nanoparticles carrying radioisotopes to augment radiotherapy, vehicle delivery systems for experimental drugs, and self-assembling nanoparticles for imaging therapeutic response to chemotherapy.

• **Engineered Nanomaterials:** The National Institute of Environmental Health Sciences (NIEHS) is supporting research to understand the interactions between engineered nanomaterials (ENMs) and biological systems to gain a fundamental understanding of the molecular and pathological pathways involved in mediating responses to ENMs.

### Key Technical Accomplishments by NNI Goal

**Goal 1. Advance a World-Class Nanotechnology Research and Development Program**

**Nanotechnology Workshop for Infectious Diseases:** Under NNI goals 1 and 2, NIAID’s VTRB organized and chaired the 2nd Nanotechnology Workshop for HIV, RNA, Infectious Diseases and Vaccine Delivery, September 25–26, 2017. The objective was to provide impetus to innovative and enabling nanotechnologies and drug delivery systems as a platform for vaccine/immunogen delivery that can greatly accelerate next-generation prophylactic and therapeutic vaccine development. This multidisciplinary meeting focused on discussion and exchange of ideas in diverse areas of vaccination, innovative therapies, and delivery systems for development of new-generation vaccines against prevalent and emergent infectious diseases including HIV.\(^2\)

**Biosensors in the Oral Cavity:** NIDCR funded four new projects in 2017 under this Funding Opportunity Announcement (FOA) (RFA-DE-17-005\(^3\)/RFA-DE-17-004\(^4\)) to encourage basic development of biosensor technologies for use in the oral cavity. These projects aim to address key research and clinical questions surrounding bone resorption in periodontitis, dynamic periodontal mechanobiological activity, and melatonin and cortisol levels in saliva within the oral cavity.

**Goal 2. Foster the Transfer of New Technologies into Products for Commercial and Public Benefit**

**Design and Development of Novel Dental Composite Restorative Systems:** This NIDCR U01 cooperative agreement includes six different projects led by prominent U.S.-based research groups. The U01 projects are currently on their fifth year of NIDCR funding. Investigators have demonstrated improvement in mechanical performance of novel dental materials that combine nanoparticle-based biomaterials with a variety of

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\(^1\) [https://dctd.cancer.gov/](https://dctd.cancer.gov/)
\(^3\) [https://grants.nih.gov/grants/guide/rfa-files/RFA-DE-17-005.html](https://grants.nih.gov/grants/guide/rfa-files/RFA-DE-17-005.html)
polymer resins. An annual Symposium and in-person Food and Drug Administration (FDA) interactions were held in FY 2017—among grantees, FDA staff members, and industry experts—for a scientific, industry, and regulatory perspective to determine a strategic framework to accelerate development and clinical translation.

**Dental, Oral and Craniofacial Tissue Regeneration Consortium (DOCTRC):** NIDCR launched Stage 2 of this initiative: RFA-DE-17-001,\(^5\) by supporting two Resource Centers (RCs) to deliver technical support, research capacity, administrative infrastructure and regulatory expertise for the DOCTRC. RCs will facilitate development of promising strategies, including nanotechnology-based strategies, for regeneration and DOC tissues to advance to clinical trials.

**Interagency Agreement (IAA) between NIDCR and the National Institute of Standards and Technology (NIST):** This IAA supports development of performance-based, clinically-relevant standards for dental materials, including nanomaterials for applications in the oral environment. Key technical achievements for this period include development of the NIST Standard Reference Instrument 6005 Polymerization Stress Tensometer (SRI 6500 PST) for inter-comparability testing during development of nanomaterial-based dental composites and development of standards for determining key polymerization properties for photopolymerized dental materials. Other accomplishments in FY 2017 include advances towards the development of a nanoscale carbonated apatite material mimicking human dental enamel that may find use as a Standard Reference Material.

**Goal 3. Develop and Sustain Educational Resources, a Skilled Workforce, and a Dynamic Infrastructure and Toolset to Advance Nanotechnology**

**Nanotechnology Research Infrastructure, Training, and Instrumentation:** NIH has a long-standing practice of addressing infrastructure needs through funding mechanisms. This includes information technology R&D, computing-enabled communications, and educational resources. Many NIH institutes support training through networks and centers funded to achieve their mission-specific goals. For instance, the NIH/NCI Cancer Nanotechnology Training Centers provide graduate and post-graduate training to researchers from diverse disciplinary backgrounds in the use of nanotechnology as an enabling tool for cancer biology and oncology research. More details on nanotechnology projects that impact the workforce can be found on the NIH reporting system: RePORT.

**Goal 4. Support Responsible Development of Nanotechnology**

**Nanotechnology Health Implications**

The NIEHS National Toxicology Program (NTP) completed an evaluation of the immune system impact of inhalation of multiwalled carbon nanotubes in rodent models to better understand the potential health effects from low-dose exposures in workers. This research complements exposure assessment of nanomaterial manufacturing facilities conducted in collaboration with NIOSH. NTP initiated (in mid-2016) a two-year chronic toxicity evaluation of multiwalled carbon nanotubes in rodent models to better understand the potential health effects from low-dose “lifetime” exposures. FDA and NTP continued collaborative efforts to understand the health hazards of nanomaterials (hazard assessment) and to develop novel methods and approaches for detection of nanomaterials in FDA-regulated products. This included physicochemical characterization and standards development processes to enable responsible development.

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development of nanotechnology. Standards are critical for the responsible development of nanotechnology-derived products from the standpoints of safety and efficacy.

The Nanotechnology Health Implications Research (NHIR) consortium, established in September 2016 (through two funding opportunities (RFA-ES-15-013 and RFA-ES-15-012), consists of nine academic research laboratories across the United States (Harvard University, UCLA, UC Davis, University of Iowa, Battle-PNNL, RTI, UC Riverside, Oregon State University, and WYSS Institute for Biologically Inspired Engineering). The NHIR consortium had its first meeting and developed plans to prioritize the criteria for selection of sets of ENMs—present in consumer products as well as emerging two-dimensional (2D) and three-dimensional (3D) materials—to be investigated by using a wide range of test systems reflecting physiologically relevant models using diverse routes of exposure (inhalation, ingestion, and ocular). In the first year, NHIR research efforts focused on developing biological response profiles for 15 ENMs of diverse physicochemical properties; these research findings are being published.

**Plans and Priorities by Program Component Area (PCA)**

NIH nanotechnology programs and projects awards contribute to all five NNI PCAs. NIH continues to participate in two of the Nanotechnology Signature Initiatives (NSIs)—the Nanotechnology Knowledge Infrastructure and Sensors NSIs—through workshops, webinars, and manufacturing consortia. NIH will continue to develop strategies to enhance knowledge through greater data collection, sharing, and tool development. PCA 2 (Foundational Research) is NIH’s second largest PCA investment area within the NNI. This investment reflects the discovery and understanding of scientific principles in medical research supported throughout the NIH institutes. NIH has provided funds for nanotechnology-related proposals covering all the major diseases (e.g., cardiac, cancer, diabetes, kidney, etc.). Nanotechnology-enabled applications, devices, and systems is the largest PCA in the NIH reported investment portfolio. Programs and projects in PCA 3 include medical devices, nanotherapeutics, drug delivery systems, and novel radiotherapeutics, supported through several FOAs renewed in FY 2016–2018. NIH provides funds for resources centers in cardiac, cancer, dental, and other clinical research areas.

A select number of nanotechnology-related initiatives that NIH established and anticipates continued support for through 2019 are presented below:

- **Nanotechnology Startup Challenge in Cancer (NSC2)**: This is an open innovation startup collaboration between the Center for Advancing Innovation (CAI) and NIH—specifically NCI and two other NIH institutes (the National Institute of Biomedical Imaging and Bioengineering and the National Heart, Lung, and Blood Institute)—to commercialize cancer nanotechnology inventions originally conceived at NIH. Twenty-eight teams were accepted to participate in the challenge at Phase 1. Of those, the top 10 teams advanced past stage 2. The NIH Office of Technology Transfer and the NCI Alliance for Nanotechnology in Cancer program office have been involved in all stages of the challenge,

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6 For a complete list of NNI goals and PCAs, see: https://www.nano.gov/about-nni/what/vision-goals.

7 http://www.nscsquared.org/

8 http://www.prweb.com/releases/2016/04/prweb13312920.htm#

9 http://www.prweb.com/releases/2016/07/prweb13575946.htm
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contributing to the strategy formulation and evaluating the startups’ licensing applications to determine the viability of commercialization and development plans.

- **NCI Alliance for Nanotechnology in Cancer:** NCi’s Alliance program pioneers the development and deployment of nanotechnology-based diagnostics and therapeutics for cancer. In 2015, NCI announced awards to six Centers of Cancer Nanotechnology Excellence (CCNEs), seven Innovative Research in Cancer Nanotechnology (IRCNs) awards, and five Cancer Nanotechnology Training Centers (CNTCs). The program will continue to execute its research and translational goals. The newly announced Funding Opportunity on Innovative Research in Cancer Nanotechnology (IRCN, R01 grants) is focused on mechanistic studies towards revealing and enhancing fundamental understanding of mechanisms behind in vivo delivery of nanoparticles and operation of in vitro nanodevices. The first grant receipt date resulted in over 80 submissions, which will be reviewed in March 2018.

It is important to note that the management of the Alliance program now resides within the Nanodelivery Systems and Devices Branch within NCI’s Cancer Imaging Program, Division of Cancer Treatment and Diagnosis. Staff members from the Office of Cancer Nanotechnology operating under NCI’s Office of the Director were brought into the Cancer Imaging Program in 2017. This transition does not impact the management of the Alliance program nor its continuation. It creates the opportunity to promote the use of nanotechnologies in fundamental studies of cancer biology and in the development of new cancer interventions related to in vitro diagnosis, imaging, and treatment of cancer.

**NCI Highlights**

The following are two programmatic highlights (accomplishments) from the Alliance program that support PCA 2 and PCA 3, respectively:

- **Multimodal nanoimaging in cancer with a transrectal ultrasound and photoacoustic device:**
  (Stanford University Center of Cancer Nanotechnology Excellence)

  **Innovation.** Development of novel nanoscale agents for anatomical, functional, and molecular imaging of prostate cancer with a transrectal ultrasound and photoacoustic device. The standard procedure for prostate cancer diagnosis, the transrectal biopsy, is invasive and cannot immediately assess for malignancy. At the same time, contemporary imaging techniques provide only anatomical references. Researchers at the Stanford University Center of Cancer Nanotechnology Excellence developed a combined real-time transrectal ultrasound and photoacoustic (TRUSPA) device. Photoacoustic imaging (PAI), combined with ultrasound, is an attractive and promising solution, where a short light pulse incident on the target tissue causes rapid heating and thermal expansion capable of acoustic detection. It is a “light in, sound out” procedure versus “sound in, sound out” of

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conventional ultrasound. In this dual modality approach, an anatomical feature such as lesion size is extracted from ultrasound, while functional information (angiogenesis) comes from PAI, with molecular information originating from both ultrasound and PAI. The operation of TRUSPA is supported by novel, nanotechnology-based contrast agents involving nanobubbles targeting gastrin-releasing peptide receptors (Figure 1), and in vivo self-assembling molecules, targeting the enzymatic activity of heparanase.

**Commercial/clinical outlet.** The TRUSPA device has been recently approved for clinical use, and the corresponding diagnostic nanomaterials are being discussed in pre-Investigational New Drug (IND) meetings with FDA for use in prostate cancer patients. Applications are also being pursued for the nanoparticles to other cancers currently assessed with ultrasound (liver, ovarian, pancreatic). This research group has been funded through the Alliance program’s U54 CCNEs for all three phases. Throughout this time, the team has developed and translated many diagnostic devices and early detection modalities, including the one discussed above.

- **Nanoscale metal-organic frameworks for light-triggered and x-ray-induced photodynamic therapy:**

  (University of Chicago, Department of Chemistry, and University of Chicago Medicine)

  **Innovation.** Development of tunable nanomaterials for enhanced x-ray-inducible deep tissue photodynamic therapy (PDT) and radioimmunotherapy. A team of researchers at the University of Chicago has been developing nanoscale metal organic frameworks (nMOFs) that are a robust bottom-up approach to designing highly porous and synthetically tunable nanomaterial photosensitizers for PDT and radiotherapy applications (Figure 2). It offers an abundance of controllable chemical properties (e.g., ligand lengths, metal atom properties, and particle morphologies) that can be optimized for specific applications. In recent years, the effort has focused on two applications for nMOFs: x-ray-inducible PDT and radioimmunotherapy. PDT is limited to superficial tumors (<1 cm in depth), due to the light source used (near infrared). The nMOFs were designed to generate x-ray-inducible singlet oxygen for use in deep tissue indications. To date, this deep tissue platform has displayed high efficacy at very low x-ray dosage (0.5 Gy/fraction) in several mouse models.

  **Clinical/commercial outlet.** nMOFs are versatile and scalable, being easily coupled to additional therapeutics and/or diagnostics with only minor adjustments to the synthetic methods needed. The platforms are robust and crystalline and thus are not a challenge to manufacture to clinical scale. The technology was licensed out to RiMO Therapeutics for further development and commercialization. The first clinical candidate from RiMO Therapeutics is being tested on patients with advanced tumors (NCT03444714). 11

**The NIEHS Nano Safety Program**

Nanotechnology-related EHS (nanoEHS) research is also an active area at NIH, and is led by NIEHS. NIH/NIEHS research efforts are designed to gain a fundamental understanding of the molecular and pathological pathways involved in mediating responses to engineered nanomaterials. To continue the

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success achieved with a small library of ENMs, centers for nanotechnology health implications research will continue to be funded through two NIEHS funding opportunity announcements through 2021. The NIEHS National Toxicology Program will also continue to conduct research in collaboration with FDA to understand the health hazards of nanomaterials and to develop novel methods and approaches for detection of nanomaterials in FDA-regulated products. In addition, the NHIR consortium research efforts will be expanded to include an additional 20 ENMs, including 2D and 3D graphene, graphene oxide, nanocellulose, and other anisotropic ENMs. Work on these ongoing projects will continue into FY 2019.

**NIDCR Dental and Craniofacial Program**

NIDCR will continue to invest in nanotechnology-based initiatives to produce novel structures that induce regeneration and repair of biological tissues, deliver biomolecules, and other research areas in support of its mission. Key plans for this program are as follows:

- **For PCA 1:** In 2016 NIDCR issued a new Request for Applications (RFA) entitled Biosensors in the Oral Cavity to support development of biosensors aimed to assess and monitor health and disease states in the oral cavity and in the whole body. Meritorious applications received in response to this RFA were funded in FY 2017 for 2-5 years in duration, as described above. This work will be powered by recent progress in wireless technologies, dissolvable nanotechnology-based electronics, microfabrication, and nanofabrication, as well as improved sensing and drug delivery, among other advances. This initiative aims to support the development of new or adaptation of existing biosensors for noninvasive, dynamic, real-time monitoring of physiological processes in the human body using the oral cavity as the sensing site. The biosensors will cover a broad range of areas in nanotechnology and nanomaterials to address mechanical, chemical, and microbial challenges imposed by the oral environment. Development of these biosensors will include design verification and validation, as well as preclinical safety testing to facilitate the translation of the oral biosensors into clinical practice.

- **For PCA 2:** In FY 2017 NIDCR continued its support of the Design and Development of Novel Dental Composite Restorative Systems Cooperative Agreement Program. The goal of this program is to enable design and development of novel dental composite materials that demonstrate superiority in material properties and durability in the oral environment over the currently utilized dental composites. In FY 2017, the 4th annual symposium was held with the research teams to evaluate technical progress by an external committee with clinical, industry standards, and product development expertise. Additionally, “pre-submission” meetings between research teams and the FDA were also arranged to solicit FDA’s feedback on the regulatory requirements and performance testing needed to ensure safety and effectiveness of the dental materials under development. The investigators demonstrated improvement in mechanical performance of their dental materials that combine nanoparticle-based biomaterials with a variety of polymer resins. These newly-developed dental materials exhibit valuable features such as self-healing and anti-microbial properties. Further development of these biomaterials is expected to generate dental composites with superior biocompatibility, ease of clinical handling, and durability. In FY 2017 and FY 2018 the investigators will continue to optimize the nanoscale properties of their candidate dental composites by taking advantage of the feedback they received from the external panel of experts and the FDA.

- In FY 2017, NIDCR launched Stage 2 of a three-stage effort to support establishing multidisciplinary resource centers (RCs) for the Dental, Oral, and Craniofacial Tissue Regeneration Consortium
This effort will extend over next 7-8 years to the current RC Development Stage (Stage 2) and the Consortium Stage (Stage 3). Stage 2 of the DOCTRC was built on the activities of Stage 1, which was launched in FY 2015. In Stage 2, the RCs will deliver technical support, research capacity, administrative infrastructure, and regulatory expertise for the DOCTRC and will facilitate advancing to clinical trials promising technologies, including nanotechnology-based technologies, for regeneration and reconstruction of DOC tissues. The overall outcome of DOCTRC will be the development of tissue engineering and regenerative medicine products, including combination products, biologics, and/or devices and associated protocols ready for the initiation of Phase 1 clinical trials. Many individual DOCTRC projects supported by the RCs will utilize nanotechnology-based strategies, thus facilitating introduction of nanotechnology into clinical practice. Examples of such products/devices include tissue regeneration enhancing scaffolds, drug delivery systems, and “smart materials” that respond to cues from the tissue microenvironment, as well as nanomaterial-based imaging modalities and biosensors.

- In FY 2017, 2018, and for the next 2-4 years NIDCR has been participating in a new trans-NIH RFA led by NIH’s National Center for Advancing Translational Sciences entitled The Microphysiological Systems (MPS) for Disease Modeling and Efficacy Testing. This initiative will support studies to develop micro- and nanoscale in vitro microphysiological system platforms (also known as tissue chips), and to validate these platforms for their ability to mimic physiological functions of human tissues and organs. This nanomedicine effort (executed in partnership with the Department of Defense, FDA, and pharmaceutical industry) supports studies to demonstrate the functional utility of the tissue chips for disease modeling to understand disease mechanisms and to identify novel therapeutic targets and treatments to inform design of clinical trials. It also leverages previous NIH investments in this field. Technologies developed under the previous and the current initiative utilize multidisciplinary approaches combining an array of nanotechnology-based strategies across fields of bioengineering, biology, microfluidics, material science, “omic” sciences, and clinical science, among others. NIDCR supports meritorious applications for development of tissue chip platforms relevant to the Institute’s mission areas.