# PROGRESS AND PLANS OF NATIONAL NANOTECHNOLOGY INITIATIVE (NNI) AGENCIES

January 2020

## Department of Health and Human Services (HHS)[1]

### *National Institutes of Health (NIH)*

#### 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 on advancing new medical diagnostics, therapeutics, and vaccines; 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 funding opportunity announcements (FOAs) supported by a large number of NIH institutes.

#### Plans and Priorities

##### National Cancer Institute (NCI)

NCI established the Alliance for Nanotechnology in Cancer (ANC) program and funded a network of awards, including U54 Centers of Excellence (Centers of Cancer Nanotechnology Excellence—CCNEs), smaller U01 and R01 grants (Innovative Research on Cancer Nanotechnology—IRCN awards), as well as training awards. NCI also supports the Nanotechnology Characterization Laboratory (NCL), an intramural laboratory located at the Frederick National Laboratory for Cancer Research.

Grants funded under the ANC program have been very productive, both scientifically and translationally. Some entrepreneurial Alliance investigators have established small companies to move technology developed in academia to translational and commercial stages. These efforts have demonstrated the potential of nanomedicine in the clinic, but also stressed the ongoing need for support of maturing innovative technologies when they move towards the translational stage.

NCI has developed internal infrastructure to aid translation and data sharing in cancer nanotechnologies. The Nanotechnology Characterization Laboratory supported the characterization of several nanomaterial formulations developed by grantees of the program as well as other researchers representing academia,

industry, and government. Overall, NCL has evaluated close to 400 different nanoparticle formulations to date. NCI also established the Translation of Nanotechnology in Cancer (TONIC) consortium to bring together several large pharmaceutical and biotechnology companies interested in nanotechnology with academic and small business researchers to discuss effective translational and commercialization strategies. Finally, the caNanoLab database was designed to house nanomaterials data; it currently holds 70 assay protocols, over 1,300 curated nanomaterial samples, and over 2,000 publications that are available to the public.

The ANC program has enhanced the influx of creative nanotechnologies into cancer research and oncology. After 15 years of operation, NIH funding for the CCNE centers will expire at the end of fiscal year (FY) 2020.[2] Thus, the only ongoing and active NCI FOA concerning nanotechnology is PAR-17-240, Innovative Research in Cancer Nanotechnology.[3] Its purpose is to continue support of research projects that are focused on the fundamental understanding of nanomaterial and nanodevice interactions with biological systems. The FOA stresses the need for innovative use of nanotechnology to solve compelling cancer biology and oncology problems rather than innovation in nanotechnology itself.

Despite the limited number of nanotechnology-centric FOAs, NCI has been attracting a growing number of grant applications in this space (with the majority of them being submitted via parent R01s as investigator-initiated applications). The number of NCI nanotechnology R01 applications has been increasing steadily and reached over 700 applications in 2018 (with 49 of those grants being funded). This is a welcome increase, demonstrating interest and the viability of implementing new technologies into cancer research and care. Initially, the majority of nanotechnology R01 submissions were reviewed by the Nanotechnology (NANO) Study Section (formed in 2008). However, as nanotechnology approaches became more mature and were shown to have broader utility, several incoming nanotechnology R01s have started to be assigned to other study sections: Gene and Drug Delivery Systems (GDD), Clinical Molecular Imaging and Probe Development (CMIP), Developmental Therapeutics (DT), and Radiation Therapeutics and Biology (RTB), indicating growing acceptance of highly innovative nanotechnologies into biomedical research.

*NCI Small Business Innovation Research (SBIR) Examples*

- Clinical Investigation of the Ceramide Nanoliposome (CNL) for Advanced Solid Tumors (1R44CA195793-01[4]). CNL was found to be highly efficacious, inducing tumor regression in hepatocellular carcinoma (HCC) animal models without systemic toxicity. The preclinical development portfolio for the CNL included evaluations of pharmacokinetics, biodistribution, metabolism, efficacy, safety, and toxicology and is available already in the literature. This R44 grant is evaluating the clinical utility of the CNL. The team of NCI-designated cancer centers led by the University of Maryland Greenebaum Comprehensive Cancer Center (UMD-GCC), in cooperation with the University of Virginia Cancer Center (UVACC) and the Fred Hollings Cancer Center at the Medical University of South Carolina (MUSC), has been assembled to conduct the proposed multi-site Phase I clinical trial. This open-label,

[2] https://www.ncbi.nlm.nih.gov/pubmed/31442467

[3] https://grants.nih.gov/grants/guide/pa-files/par-17-240.html; subsequently re-issued as PAR-20-284, https://grants.nih.gov/grants/guide/pa-files/PAR-20-284.html

[4] https://www.sbir.gov/sbirsearch/detail/1046851

dose escalation study is designed to establish the safety of the CNL and recommended parameters for a Phase II clinical trial.

- A Novel Targeted Nanomedicine Delivering MicroRNA-30-5p Replacement Therapy for Multi-Drug Resistant Cancer Treatment (1U43CA221567-01[5]). This grant is focused on the development of a microRNA-based therapeutic mimic of miR-30-5p (miRecule candidate MC-30) for the treatment of multi-drug resistant (MDR) cancers. miR-based therapeutics offer a disruptive MDR cancer treatment by targeting both the primary oncogenic pathways and potentially suppressing mechanisms of intrinsic or acquired resistance. A significant hurdle for nucleic acid therapeutics is a lack of an efficient means of delivering them specifically to target cancer cells, especially at the metastatic stage. To overcome this obstacle, the company will employ chemical modification of the mimic construct to improve nuclease stability and activity and then encapsulate it in a clinically validated tumor-targeted liposomal nanodelivery system (scL). These constructs are being tested in a cetuximab and cisplatin-resistant orthotopic xenograft mouse model of head and neck squamous cell carcinoma (HNSCC) and compare directly with standard of care cisplatin and cetuximab.

### National Heart, Lung, and Blood Institute (NHLBI)

NHLBI does not currently have any programs focused specifically on nanotechnology. A few highlights originating from investigator-initiated grants are given in the next section. These efforts entail the development of targeted nanomaterials for the diagnosis and/or treatment of cardiovascular, lung, and blood diseases, and in particular the development of nanomaterials as artificial blood substitutes, nanostructured surface coatings on mechanical devices to reduce thrombosis and/or infection, and nanoscaffolds to promote myocardial regeneration.

*SBIR/STTR Funding*

NHLBI funds a number of nanotechnology-related Small Business Innovation Research and Small Business Technology Transfer (STTR) grants at various stages of development. An example of a relatively mature application is R44 HL131169, High-Throughput NanoMEA-Based Proarrhythmia Assay.[6] Undetected arrhythmia-inducing effects in new drugs frequently leads to failure at late stages of development or drug withdrawal from the market. As a result, FDA[7] mandates that all new drugs be tested for potential arrhythmogenic properties, which has led to a growing market for accurate and cost-effective preclinical screening tools. Human pluripotent stem cell-derived cardiomyocytes offer the potential to generate superior *in vitro* cardiac tissues for such applications, but their utility is limited by inadequate maturation of the tissues. This award supports development of a 384-well nanopatterned microelectrode array capable of promoting and measuring the functional development of mature human cardiac tissue. This will enable more accurate and predictive screening of drug effects on human cardiac performance prior to advancement to clinical trials, streamlining drug development protocols and bringing new drugs to the market more quickly.

[5] https://www.sbir.gov/sbirsearch/detail/1324983

[6] https://www.sbir.gov/sbirsearch/detail/1570991

[7] For a list of other Federal agencies participating in the NNI, and their abbreviations, see https://www.nano.gov/partners.

## National Institute of Environmental Health Sciences (NIEHS)

Nanotechnology-related environmental, health, and safety (nanoEHS) research efforts are designed to gain a fundamental understanding of the molecular and pathological pathways involved in mediating biological responses to engineered nanomaterials (ENMs). These efforts are supported through a robust extramural research program, intramural contract research, and development of tools and devices needed through SBIR/STTR programs. The Nanotechnology Health Implications Research (NHIR) consortium, initiated in 2016, will continue to be funded through 2021. The research efforts across these centers continue to evaluate ENM-biological interactions using diverse *in vitro*, tissue-on-chip, and *in vivo* models. To date, studies were focused on more than 40 ENMs ranging from metal and metal oxide ENMs known to be present in diverse consumer products and emerging anisotropic ENMs such as graphene, graphene oxide, metal-graphene hybrids, and nanocellulose. Examples of ongoing and planned activities include the following:

- The NIH/NIEHS National Toxicology Program has 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. Work on this project will continue into FY '21. Also, studies initiated on multiwall carbon nanotube chronic cancer bioassays in rodent models will be continued in FY '21.
- Collaborative efforts with FDA under the National Toxicology Program will also continue.
- The NIEHS Superfund Research Program plans to emphasize research that includes nanotechnology-enabled structures to enhance sustainable remediation.
- NIEHS is also actively participating in the NNI-supported interagency working group on nanoplastics.

*SBIR/STTR Funding*

The NIEHS small business program continues to solicit applications to support development of tools, technologies, and assays for medium- to high-throughput screening for safety evaluation of ENMs with potential commercial use. This is being accomplished through including nanoEHS-relevant activities in the Omnibus solicitation for SBIR and STTR grants.[8] NIEHS released an FOA in FY '18 to support the development of tools for monitoring personal exposure and response to ENMs in the environment, and has funded four Phase I projects through that FOA:

- Developing an organotypic intestinal tissue model to detect ENMs that cause gastrointestinal irritation, inflammation, or genotoxicity.
- An air-liquid interface model for ENM toxicity in nasal epithelial cells.
- A field-deployable device that captures ENM particles and tests for toxicity in an *in vitro* system using lung epithelial cells.
- An evaluation protocol for exposure characterization from ENMs in consumer products using mass spectrometry and Raman spectroscopy.

Beginning in FY '21, the SBIR efforts of the NIEHS Superfund Research program will be supporting development of nanotechnology-enabled structures to enhance sustainable remediation.

[8] https://sbir.nih.gov/sites/default/files/2019-2_SBIR-STTR-topics.pdf, page 106-107

### National Institute of Allergies and Infectious Diseases (NIAID)

The institute conducts advanced development of multiple nanotechnology-based HIV vaccine platforms/products for clinical studies. It also fosters innovative/promising nanotechnology platforms by providing funding/seed investment to academic investigators and biotechnology companies to support early-stage R&D with commercial potential. NIAID has a dedicated U19 program: Integrated Preclinical/Clinical AIDS Vaccine Development (IPCAVD),[9] funds investigator-initiated R01s, and operates an SBIR program.

The goal of the IPCAVD program is to facilitate the translation of sufficiently advanced, innovative, and promising vaccine candidates into early clinical testing. The program has been 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.

*SBIR/STTR Examples and Highlights*

PHS 2019-1 SBIR Topic 064 | Particle-based Delivery of HIV Env/Protein Antigens:

- A Liposomal Platform for Spontaneous, Particleized Presentation of HIV Trimer lmmunogens.[10] This award is supporting development of a vaccine against HIV-1 by combining two promising technologies: (a) spontaneous nanoliposome antigen particleization (SNAP), which is a novel method for attachment of proteins to immunogenic nanoliposomes to produce powerful adjuvants, and (b) native flexibly linked (NFL) trimers of HIV-1 Env (e.g., BG505, 16055, and 1086c), which are state-of-the-art antigens for HIV vaccine development. Phase I activities ongoing.
- DNA Based Nanoparticle Platform for HIV Env Presentation.[11] In collaboration with Scripps Research Institute, this project proposes to produce an HIV-1-1 vaccine composed of a structured DNA origami nanocarrier for delivery of a stabilized native flexibly linked trimer envelope glycoprotein with an integrated TLR-9 immunostimulatory adjuvant (CpG ODN). DNA origami is customizable (both chemically and structurally) and thus offers a highly tunable platform for spatial organization of biomolecules such as HIV-1-1 Envs. Phase I activities ongoing.
- Nanoparticle Delivery of HIV Env Trimer for Inducing Somatic Hypermutation and bNab.[12] This project is developing a proprietary engineered CHO cell line to express sialylated HIV-1-1 Env trimer and deliver it through gold nanoparticles. It will engineer molecular adjuvant C3d (complement cleavage fragment component) to be co-displayed with Env on nanoparticles to enhance the B-cell interaction with the host immune system. Phase I activities ongoing.
- New Carriers Used as Adjuvants for Controlled HIV Immunogen Delivery into Targeted Antigen Presenting Cells.[13] This project is using mesoporous silica nanoparticles (MSNPs) with mannose-targeting as both a delivery vehicle to antigen presenting cells (APCs) and for its adjuvant properties. The MSNPs will be capped with a pH-sensitive polymer that is designed to remain closed in the extracellular space and open upon reaching the lower pH of the endosomes of the APC for release of

[9] https://grants.nih.gov/grants/guide/pa-files/PAR-15-330.html

[10] https://www.sbir.gov/sbirsearch/detail/1675347

[11] https://www.sbir.gov/sbirsearch/detail/1675341

[12] https://www.sbir.gov/sbirsearch/detail/1675281

[13] https://www.sbir.gov/sbirsearch/detail/1675305

mRNA (generating a native membrane-bound HIV Env, gp160) and TLR-4/TLR-9 agonist cargo. Phase I activities ongoing.

### National Institute of Dental and Craniofacial Research (NIDCR)

The National Institute of Dental and Craniofacial Research has continued several strategic investments in nanotechnology-based initiatives to support its broad mission of improving dental, oral, and craniofacial (DOC) health. NIDCR leverages its investments on the significant promise of nanotechnology as 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.

Additional areas of NIDCR-supported research in nanotechnology focus on the development of oral biodevice technologies for the evaluation, monitoring, and management of oral and overall health; development of high-performing dental materials for the restoration, repair, and replacement of DOC tissues; and development of clinically relevant standards for dental materials, including reference materials and quality guidance to research and product manufacturing. Lastly, NIDCR supports projects investigating chemical and physical properties of dental nanomaterials for diagnosis and treatment of disease, as well as nanomaterials for bioimaging applications, and nanomaterials for implants and functionalized surface coatings.

## Key Technical Accomplishments

### National Cancer Institute

- Spherical nucleic acids (SNAs), which have been developed in Chad Mirkin's group at Northwestern University, have found their way into developing new strategies for cancer vaccines. It appears that SNA structure has a critical influence on immune-stimulatory performance, in particular the position and conjugation chemistry of the peptide antigen within SNA. Mechanistic studies on the synthesis of different structures have led to the approach of "rational vaccinology with spherical nucleic acids,"[14] which will allow predicting effectiveness of different SNA designs in immunotherapy. A spin-off company pursues commercialization of SNA-based vaccines.[15]
- Wenbin Lin and Ralph Weichselbaum at the University of Chicago have been developing nanoscale metal–organic frameworks (nMOFs) and coordination polymers (NCPs). These constructs enhance the efficacy of x-ray radiotherapy via the radiotherapy-radiodynamic therapy (RT-RDT) mode of action. They are intrinsically nontoxic and greatly reduce x-ray doses needed to eradicate local tumors in mouse models. The technology is being commercialized;[16] the "RiMO" technology combines multiple therapeutic modalities to increase efficacy while simultaneously reducing toxicity.
- Mark Grinstaff and colleagues (Boston University) are exploring an entirely new approach called "materials-based targeting" to enhance intraperitoneal drug delivery for treatment of mesothelioma. This new delivery scheme relies on pH-responsive "expansile" nanoparticles (eNPs) that swell in the acidic tumor microenvironment and "lodge" in tumors for prolonged drug release. This delivery approach will be studied to determine how chemical properties, nanoarchitecture, and drug incorporation into eNP complexes impact tumor specificity and intracellular trafficking.

[14] https://www.ncbi.nlm.nih.gov/pubmed/31068463

[15] http://www.exicuretx.com/

[16] http://www.rimorx.com/about/

## National Heart, Lung, and Blood Institute

NHLBI examples below are drawn from investigator-initiated grants and are as follows:

*Atherosclerosis Nanotherapy*

Simvastatin-loaded high-density lipoprotein nanotherapeutics have shown potential for reducing chronic inflammation in atherosclerosis in rodent models. However, translation of these technologies towards clinical use poses significant challenges in scale up, and in monitoring therapy delivery and efficacy. Researchers at the Icahn School of Medicine and colleagues successfully scaled up production of nanomaterials to quantities needed for larger animals (rabbits and pigs), and developed translational imaging protocols to monitor the effects of nanoimmunotherapy treatment on inflammation. They were able to demonstrate that nanoimmunotherapy reduced inflammation in large animals, halting progression of atherosclerotic plaque, and supporting the translatability towards clinical use to treat atherosclerosis.[17]

The efficacy of nanotherapeutics to reduce atherosclerotic plaque burden can be potentiated using nanocarriers that sense and respond to the diseased microenvironment. Researchers from UNC Chapel Hill and colleagues developed a technique for using an apolipoprotein-A1 mimetic targeting peptide to deliver a pro-resolving therapeutic derived from annexin-A1 to atherosclerotic plaque on a peptide amphiphile scaffold. The therapeutic is tethered to the scaffold with a peptide linkage cleaved by enzymes found in the atherosclerotic niche, facilitating delivery of the therapeutic where it is needed to decrease macrophage activation and reduce inflammation.[18]

*Wound Healing*

Chronic wounds, which frequently occur, for example, in patients with critical limb ischemia, can lead to severe complications, including limb amputation and death. These wounds are characterized by impaired healing and uncontrolled inflammation, which compromise the protective role of the immune system and may lead to bacterial infection. Polarization of macrophages toward the anti-inflammatory (M2) phenotype can accelerate wound healing, a process that can be driven by micro-RNA (miR-223). Investigators from UCLA and colleagues developed adhesive hydrogels containing miR-223 5p mimic (miR-223*)-loaded hyaluronic acid nanoparticles to control tissue macrophage polarization during wound healing. The hydrogels adhered to and covered wounds in an acute wound model, and efficiently promoted the formation of uniform vascularized skin at the wound site through macrophage polarization, demonstrating the potential of nanoparticle-laden hydrogels delivering miRNA-223* to accelerate wound healing.[19]

*Iron Chelation*

Patients with transfusion-dependent hemoglobinopathies are at risk of iron overload, which can increase the risk of heart failure, liver cirrhosis and cancer, arthritis, dyslipidemia, and diabetes, and may be associated with several neurodegenerative diseases. Iron chelation can remove the excess iron, but small molecule-based iron chelators can cause adverse side effects such as infection, gastrointestinal bleeding,

[17] https://www.ncbi.nlm.nih.gov/pubmed/31434756

[18] https://www.ncbi.nlm.nih.gov/pubmed/30620448

[19] https://www.ncbi.nlm.nih.gov/pubmed/31328877

kidney failure, and liver fibrosis. This led investigators to develop renal clearable nanochelators with improved kidney-specific biodistribution and rapid renal excretion (>80% injected dose in 4 h), compared to the small molecule deferoxamine (DFO). Subcutaneous (SC) administration of the nanochelators further improved pharmacodynamics. Daily SC injections of the nanochelator for 5 days to iron-overloaded mice and rats decreased iron levels in serum and liver, and significantly reduced kidney damage caused by iron overload without demonstrating DFO's nephrotoxicity. This renal clearable nanochelator thus provides the potential for enhanced efficacy and safety.[20]

### National Institute of Environmental Health Sciences

NHIR consortium investigators using lab-on-chip technology developed the scatter-enhanced phase contrast (SEPC) method for monitoring active nanoparticle transport in living cells. An image from this publication was on the cover of *Nano Letters*. SEPC microscopy was adapted to serve as generalized label-free approach for monitoring nanoparticle uptake and transport dynamics. The technique is expected to advance understanding of the uptake and transport dynamics of engineered nanomaterials by mammalian cells and contribute to designing next-generation drug delivery systems. SEPC works for a variety of metal and metal oxides, including Au, Ag, $TiO_2$, $CeO_2$, $Al_2O_3$, and $Fe_2O_3$ nanoparticles.[21]

### National Institute of Allergies and Infectious Diseases

*IPCAVD Program Highlights*

- Duke University has been funded with two IPCAVD grants to develop mRNAs in lipid nanoparticles (LNPs) for mRNA administration for induction of either protective non-neutralizing antibodies (nNAbs) or broadly neutralizing Abs (bNAbs). Under this funding mechanism, the Bart Haynes group at Duke is developing process and GMP manufacture optimal mRNA immunogens and mRNA-LNP formulations for use in human Phase I trials.
- Dr. Ruth Ruprecht and Mymetics Corporation have been funded to develop and GMP manufacture a novel virosomal HIV vaccine. The product concept involves influenza virosomes enveloping virus-like particles that display on their surface elongated HIV gp41 peptides (virosome-P1) or recombinant truncated HIV gp41 (virosome-rgp41). Powdered particulate dosage forms of new virosome vaccine candidates will be GMP manufactured and administered as nasal spray.

*Preclinical HIV Vaccine Development*[22]

Process development for the first synthetic glycopeptide HIV immunogen nanoparticle vaccine has started. Chemistry and Manufacturing Controls (CMC)-compliant process and GMP manufacturing will be developed to conduct Phase 1 clinical trials. Progress on building an armamentarium of particulated adjuvants for preclinical and clinical studies includes the following:

- GMP GLA-LSQ liposomal adjuvant for antigen-adjuvant comparison clinical study. In Q1 2019, NIAID's Vaccine Translational Research Branch (VTRB) acquired this liposomal adjuvant for a Julie McElrath/HVTN clinical trial comparing a variety of adjuvants.

[20] https://www.ncbi.nlm.nih.gov/pubmed/31723130?dopt=Citation

[21] https://pubs.acs.org/toc/nalefd/19/5

[22] Support Contract HHSN272201700010I, https://beta.sam.gov/opp/a086308926c94245be9d8276c1189dfe/view

- Delta inulin (Advax™), a polysaccharide particle adjuvant. GMP manufacturing process development is ongoing to produce the adjuvant of appropriate quality to support clinical trials.

### National Institute of Dental and Craniofacial Research

*NIDCR Science Highlights*

- Biosensors in the oral cavity. In 2019 NIDCR continued to support four projects funded in 2017 under this FOA (RFA-DE-17-005 / RFA-DE-17-004)[23] to encourage basic development of biosensor technologies for use in the oral cavity. These projects implement nanomaterials and nanoscience approaches to address key research and clinical questions surrounding detection of bone resorption in periodontitis, dynamic periodontal mechanobiological activity, and measurements of melatonin and cortisol levels in saliva.
- Enabling Technologies to Accelerate Development of Oral Biodevices. NIDCR launched this initiative in November of 2018 under several FOAs (PA-19-076[24] / PA-19-075[25] / RFA-DE-19-008[26] / RFA-DE-19-009[27]). The purpose of this initiative is to encourage research in transformative engineering solutions for system-level challenges to improve the evaluation, monitoring, and management of oral and overall health using multifunctional oral biodevices. Four new research projects were funded in FY '19, out of ten applications received in response to the FOAs. Newly funded projects implement various forms of nanomaterials, nanoscience, and nanobiotechnology principles to integrate electronic, physical, and biological systems into biodevices for detection, diagnosis, and treatment of oral and systemic disease. New technologies funded under this oral biodevice initiative in FY '19 are intended for oral and overall health applications, including development of: novel high-resolution scintillation x-ray detectors for digital dentistry; enzyme-free electrochemical breathalyzer for the diagnosis and management of diabetic ketoacidosis; therapeutic microneedles for localized treatment of periodontal tissue; and a smartphone-based infrared-fluorescence-imaging intraoral device (Smart-IR-ID) for dentist-guided real-time self-monitoring of periodontal disease. These integrated oral biodevice systems would help facilitate incorporation of precision-medicine-based approaches into clinical practice. NIDCR expects to continue supporting this initiative and to fund meritorious projects in FY '20.
- Advancing Imaging, Device Production, and Clinical Capabilities in Digital Dentistry. NDICR launched this new initiative in October of 2018 under FOA PA-19-021 / PA-19-022.[28] This FOA encourages innovation, optimization, and customization of core technologies in digital dentistry that improve efficiency of oral healthcare delivery, effectiveness of clinical decision making, and outcomes of treatments of DOC tissues. Among areas of interest are development of imaging-based diagnostics and analytical techniques for dental radiology and the integration of 3-dimensional (3D) additive manufacturing (e.g., 3D printing) with imaging tools. This FOA also supports development of high-

[23] https://grants.nih.gov/grants/guide/rfa-files/rfa-de-17-004.html, https://grants.nih.gov/grants/guide/rfa-files/RFA-DE-17-005.html

[24] https://grants.nih.gov/grants/guide/pa-files/PA-19-076.html

[25] https://grants.nih.gov/grants/guide/pa-files/PA-19-075.html

[26] https://grants.nih.gov/grants/guide/rfa-files/rfa-de-19-008.html

[27] https://grants.nih.gov/grants/guide/rfa-files/rfa-de-19-009.html

[28] https://grants.nih.gov/grants/guide/pa-files/PA-19-021.html, https://grants.nih.gov/grants/guide/pa-files/PA-19-022.html

performance materials that employ nanotechnology-based additives with novel manufacturing approaches for the repair, replacement, and/or restoration of DOC tissues. Three new applications were received in response to this initiative in FY 2019, but none have been funded to date. NIDCR expects to continue supporting this initiative and to fund meritorious projects in FY 2020.

*Focused Programs and Agreements—Transferring Nanotechnologies for 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. FY 2018 was the fifth and final year of NIDCR support for these projects. Several investigators supported under the U01 program have successfully competed for new funding awards in FY 2019, including an NIDCR Award for Sustaining Outstanding Achievement in Research (SOAR) awarded to Dr. Carmem Pfeifer to continue development of novel nanomaterial-based polymeric formulations with improved durability in the oral environment (R35 DE029083).[29] Overall, outcomes from the six NIDCR-supported U01 projects demonstrated that specific improvements can be made in mechanical performance and other properties of nanoparticle-based dental restorative composites. The U01 research teams are currently pursuing pathways for commercialization of their new products by establishing small business ventures and/or licensing intellectual property to industry partners. NIDCR is committed to continue supporting development of new nanomaterial-based dental composites using established funding mechanisms.
- Dental, Oral and Craniofacial Tissue Regeneration Consortium (DOCTRC). In FY 2017 NIDCR launched Stage 2 of this initiative, RFA-DE-17-001,[30] by supporting the development of two Resource Centers (RCs) that are currently delivering technical support, research capacity, administrative infrastructure, and regulatory expertise to several dozen individual projects developing clinically-targeted approaches, including nanotechnology-based approaches, for regeneration and reconstruction of DOC tissues. Stage 3 of this initiative will be launched in the spring of FY 2020.
- Interagency Agreement (IAA) between NIDCR and NIST. This effort supports development of performance-based, clinically-relevant standards for dental materials, including nanomaterials, for applications in the oral environment. Key technical achievements for the 2019 period include participation of NIST representatives in standards development organizations, and preparation of scientific manuscripts to disseminate experimental findings on standards development for clinically relevant photo-curing modes to reduce polymerization stress of nanomaterial-based dental restorative composites. Standards development activities in FY 2019 involved attendance of NIST representatives as designated U.S. Experts on the U.S. Technical Advisory Group in the Adhesion Testing, Dental Instruments, and Biological Evaluation Working Groups (WGs) to International Organization for Standardization (ISO) Technical Committee 106 (Dentistry).[31] In the Adhesion Testing WG, standard test methods for bond strength of dental materials to teeth were discussed. The WG consensus was to withdraw outmoded standards and create new standards to reflect the current state of dental materials. The technical discussion for these new standards is scheduled for the next ISO meeting in August 2020. The Biological Evaluation WG discussed a proposal for adding rules for the generation of clinically-relevant nanoparticles from dental restorative materials as a basis for

[29] https://www.nidcr.nih.gov/grants-funding/funding-priorities/future-research-initiatives/nidcr-award-soar-r35

[30] https://grants.nih.gov/grants/guide/rfa-files/rfa-de-17-001.html

[31] https://www.iso.org/committee/51218.html

toxicological testing/evaluation. Driven by NIST researchers, the WG called for additional studies and new proposals on the biological effects of light curing units, with a focus on the potential for biological damage due to the local temperature rise and light transmission that occurs during the photocuring process in the clinic. Additionally, an approval for a final ballot of a new technical specification for polymerization stress measurement of nanomaterial-based dental composites proposed by NIST was achieved by the American Dental Association—Standards Committee for Dental Products. Four new draft manuscripts describing photopolymerization properties of nanomaterial-based dental restorative composites and the role of the light curing protocols on those properties have been completed. This work holds potential to improve overall performance of nanomaterial-based dental restorative composites to enhance clinical outcomes and provide informed guidance on best practices to manufacturers and clinicians.

*SBIR/STTR Examples and Highlights*

- R44 DE027903-02, Bioresorbable Nanoparticles for Visual Detection of Early-Stage Dental Caries.[32] This SBIR Phase II project seeks to develop a diagnostic test for use by dental professionals as part of the routine dental exam to better detect and predict progression of dental caries. The commercial product will be a mouth rinse, or oral gel product, containing small functionalized fluorescent nanoparticles made from corn starch that illuminate active enamel lesions using a standard curing lamp for early detection of caries at dental offices. Early feasibility of developing functionalized nanoparticles to selectively detect active caries *in vitro*, as well as early-stage preclinical safety of the functionalized nanoparticles, was demonstrated during SBIR Phase I. Successful completion of the Phase II will establish preclinical safety and effectiveness to facilitate further clinical development, and to achieve regulatory and manufacturing milestones. This technology has the potential to improve long-term oral health outcomes for patients through greater conservative treatment and less overtreatment of dental caries.
- R44 DE026373-02, Innovative High-Resolution Dental X-ray Imager.[33] This SBIR Phase II project is developing superior dental imaging technology to provide both high imaging resolution and efficiency, while reducing radiation dose in routine x-ray examinations. The imaging device will combine silicon-based imaging arrays and semiconductor x-ray conversion layers in the imaging detector by exploring a variety of candidate nanomaterials and coating deposition methods. Optimizing the x-ray conversion layer with mercuric iodide ($HgI_2$) has the potential to offer significant advantages over existing x-ray imagers by enabling greater dose efficiency and higher image contrast. This project seeks to advance the technology development of this dental imaging system in two primary areas: (1) optimization of fabrication and electronic properties of the films to reach better film uniformity for large-size films; and (2) merging the $HgI_2$ with complementary metal-oxide-semiconductor (CMOS) technology. If successful, this innovative imaging detector could also be used in other clinical applications, including mammography and micro-computed tomography.

### National Institute of Bioimaging and Bioengineering (NIBIB)

NIBIB nanotechnology highlights include the following:

[32] https://www.sbir.gov/sbirsearch/detail/1567205

[33] https://www.sbir.gov/sbirsearch/detail/1197271

*Tiny Generators Turn Body Motion into Weight Control and Wound-Healing Therapies: Nanogenerator's Electrical Pulses Provide Beneficial Outcomes with No Side Effects—Rat Study*

Although electrical stimulation has therapeutic potential for various disorders and conditions, ungainly power sources have hampered practical applications. Now NIBIB-funded bioengineers have developed implantable and wearable nanogenerators from special materials that create electrical pulses when compressed by body motions. The pulses controlled weight gain and enhanced healing of skin wounds in rat models.

The researchers used what are known as piezoelectric and dielectric materials, including nanoscale ceramics and crystals, which have a special property of creating an electrical charge in response to mechanical stress.

Weight loss. The researchers developed a vagal nerve stimulator (VNS) that dramatically improves appetite suppression through electrical stimulation of the vagus nerve. The VNS consists of a small patch, about the size of a fingernail, which carries the nanogenerators and is attached to the rat's stomach with minimally invasive surgery. Stomach motion from eating causes the attached nanogenerator to produce electrical pulses (Figure 1). When eating starts, the electrical pulses stimulate the vagus nerve, which tells the brain that the stomach is full (when it is not) and the animal stops eating. The device curbed the rat's appetite and reduced body weight by a remarkable 40 percent.

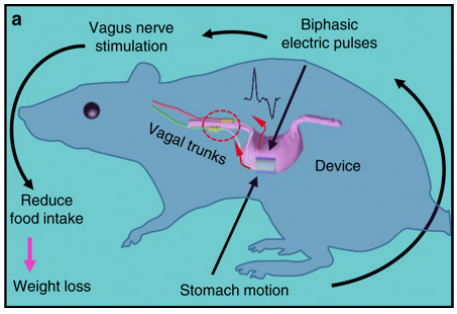


**Figure 1. Image credit: Xudong Wang, University of Wisconsin-Madison (re-used by permission from https://www.nature.com/articles/s41467-018-07764-z, open access).**

Wound Healing. Skin wounds on the backs of rats were covered by electrodes attached to a nanogenerator that wraps around the rat's chest (Figure 2) and produces electrical pulses when the rat breathes. The electrical pulses caused wounds to heal in just three days compared to two weeks with normal treatment.

The researchers observed electrical activation of normal cellular healing processes that included the movement of healthy skin fibroblasts into the wound, accompanied by the release of biochemical factors that promote the growth of the fibroblasts and other cell types that expand to repair the wound space.

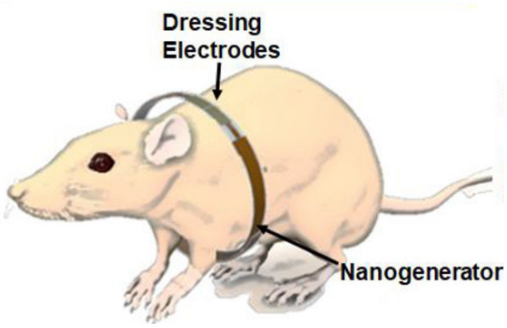


**Figure 2. Image credit: Xudong Wang, University of Wisconsin-Madison (copyright American Chemical Society; re-used by permission from https://pubs.acs.org/doi/10.1021/acsnano.8b07038).**