THE NATIONAL NANOTECHNOLOGY INITIATIVE SUPPLEMENT TO THE PRESIDENT'S 2023 BUDGET

Product of the

SUBCOMMITTEE ON NANOSCALE SCIENCE, ENGINEERING, AND TECHNOLOGY

COMMITTEE ON TECHNOLOGY

of the
NATIONAL SCIENCE AND TECHNOLOGY COUNCIL

FEBRUARY 2023

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The National Science and Technology Council (NSTC) is the principal means by which the Executive Branch coordinates science and technology policy across the diverse entities that make up the Federal research and development enterprise. A primary objective of the NSTC is to ensure that science and technology policy decisions are consistent with the President's stated goals. The NSTC prepares research and development strategies that are coordinated across Federal agencies aimed at accomplishing multiple national goals. The work of the NSTC is organized under committees that oversee subcommittees and working groups focused on different aspects of science and technology. More information is available at www.whitehouse.gov/ostp/nstc.

About the Office of Science and Technology Policy

The Office of Science and Technology Policy (OSTP) was established by the National Science and Technology Policy, Organization, and Priorities Act of 1976 to provide the President and others within the Executive Office of the President with advice on the scientific, engineering, and technological aspects of the economy, national security, homeland security, health, foreign relations, the environment, and the technological recovery and use of resources, among other topics. OSTP leads interagency science and technology policy coordination efforts, assists the Office of Management and Budget (OMB) with an annual review and analysis of Federal research and development in budgets, and serves as a source of scientific and technological analysis and judgment for the President with respect to major policies, plans, and programs of the Federal Government. More information is available at www.whitehouse.gov/ostp.

About the Subcommittee on Nanoscale Science, Engineering, and Technology

The Subcommittee on Nanoscale Science, Engineering, and Technology (NSET) contributes to the activities of NSTC's Committee on Technology. NSET's purpose is to advise and assist the NSTC and OSTP on policies, procedures, and plans related to the goals of the National Nanotechnology Initiative (NNI). As such, and to the extent permitted by law, the NSET Subcommittee defines and coordinates Federal efforts in support of the goals of the NNI and identifies policies that will accelerate deployment of nanotechnology. NSET also tracks national priority needs that would benefit from the NNI, identifies extramural activities that connect to NNI goals, and explores ways the Federal Government can advance the development of nanotechnology. More information is available at https://www.nano.gov/.

About this document

This document is a supplement to the President's 2023 Budget request submitted to Congress on March 28th, 2022, and serves as the Annual Report for the National Nanotechnology Initiative called for under the provisions of the 21st Century Nanotechnology Research and Development Act (15 USC §7501). The report also addresses the requirement for Department of Defense reporting on its nanotechnology investments (10 USC §2358). Additional information regarding the NNI is available on the NNI website at www.nano.gov.

About the cover

Outside Covers: Scientists from Brookhaven National Laboratory (BNL) and a university are exploring lithium titanate "nanoflowers" for energy storage applications. The lithium titanate material was doped using chlorine, increasing the electrical conductivity and expanding the crystal lattice of the material. The unique "nanoflower" architecture creates a larger surface area, providing multiple pathways for the lithium ions to access the material. As a consequence, the channels used for lithium-ion migration become wider, increasing the ability to quickly use and recharge the batteries for many cycles. This image was acquired using a scanning electron microscope at Brookhaven's Center for Functional Nanomaterials. The work was supported by the U.S. Department of Energy, the National Science Foundation, and university funds. See: https://www.bnl.gov/newsroom/news.php?a=217376 and https://doi.org/10.1002/chem.202002489. Image credit: BNL.

Inside Back Cover: The inside face of the back cover is a collage of images illustrating examples of NNI outreach activities. Collage content and design is by Patrice Pages and Kristin Roy of the National Nanotechnology Coordination Office (NNCO).

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EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF SCIENCE AND TECHNOLOGY POLICY
National Science and Technology Council
WASHINGTON, D.C. 20502

The National Science and Technology Council (NSTC)

February 1, 2023

Dear Members of Congress:

I am pleased to share with you the annual report for the National Nanotechnology Initiative (NNI), the *National Nanotechnology Initiative Supplement to the President's 2023 Budget*. This report highlights significant progress of the NNI in contributing to national science and technology (S&T) priorities, as well as plans for the coming year that will make important contributions to the Nation's economic prosperity, national security, and public health and well-being.

The President's 2023 Budget requests nearly $2 billion for the NNI, the largest ever request since its inception. This reflects the widespread recognition of the potential for nanotechnology to contribute to agency missions and national priorities. This report includes examples of NNI contributions to all five of the S&T priorities set out by President Biden: (1) *Pandemic preparedness:* research and regulatory review of nanotechnology-enabled COVID-19 diagnostics, vaccines, and therapeutics, including on lipid nanoparticle-encapsulated mRNA vaccines and new efforts to develop nanoparticle "universal" vaccines. (2) *Climate change:* nanomaterial-enabled photovoltaic and energy storage devices, as well as electrochromic coatings for energy-efficient windows and low-power nanoelectronics. (3) *Technologies and industries of the future:* nano-electronics, -photonics, and -magnetics research is promoting U.S. leadership in microelectronics and next-generation computing/communications, enabling advances in quantum information science and artificial intelligence. (4) *Sharing the fruits of S&T among all Americans*: nanoscale R&D infrastructure enables broad access to the resources necessary to develop nanoscale solutions, providing the opportunity for diverse community involvement and the democratization of science. (5) *Ensuring the long-term health of S&T in our Nation:* 45% of the NNI's proposed 2023 total supports basic science to enable future innovations, and contributes to progress in other S&T fields.

The investment categories and goals outlined in this report were revised for the 2021 NNI Strategic Plan, partially in response to the 2020 quadrennial review of the NNI by the National Academies of Science, Engineering, and Medicine.

This year marks 23 years since President Bill Clinton first proposed the NNI, and the 20th anniversary of President George W. Bush signing the 21st Century Nanotechnology Research and Development Act. Much has been accomplished, but there is much more to come, as the NNI continually re-invents itself in response to a changing world and rapid advancements in nanoscale science, engineering, and technology. I look forward to continuing to work with you to support the President's priorities, and the NNI's contributions to those priorities.

Sincerely,

Arati Prabhakar
Assistant to the President and
Director, Office of Science and Technology Policy

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[†] An independent commission that is represented on NSET but is non-voting

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[†] An independent commission that is represented on NSET but is non-voting

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Abbreviations and Acronyms[1]

2D	two-dimensional
3D	three-dimensional
AFRI	Agriculture and Food Research Initiative (USDA/NIFA)
AFRL	Air Force Research Laboratory
AI	artificial intelligence
AMO	Advanced Manufacturing Office (DOE)
APEC	Asia Pacific Economic Cooperation
ARO	Army Research Office
ATE	Advanced Technology Education (NSF)
BES	[Office of] Basic Energy Sciences (DOE)
BIO	[Directorate for] Biological Sciences (NSF)
CBER	Center for Biologics Evaluation and Research (FDA)
CCI	Center for Chemical Innovation (NSF)
CFSAN	Center for Food Safety and Applied Nutrition (FDA)
CNST	Center for Nanoscale Science and Technology (NIST)
CNT	carbon nanotube
DARPA	Defense Advanced Research Projects Agency
EHS	environment(al), health, and safety
ELSI	ethical, legal, and other societal implications
EMI	electromagnetic interference
ENG	[Directorate for] Engineering (NSF)
ENM	engineered nanomaterial
ERC	Engineering Research Center (NSF)
ERDC	Engineer Research and Development Center (Army)
EU	European Union
hBN	hexagonal boron nitride
HIV	human immunodeficiency virus
IDEA	inclusion, diversity, equity, and access
ISN	Institute for Soldier Nanotechnologies (Army)
ISO	International Organization for Standardization
IUCRC	Industry-University Cooperative Research Center (NSF)
JUMP	Joint University Microelectronics program (DARPA)
LNP	lipid nanoparticle
MGI	Materials Genome Initiative
mRNA	messenger RNA
MRSEC	Materials Research Science and Engineering Center (NSF)
MURI	Multidisciplinary University Research Initiative (DOD)
nanoEHS	nanotechnology environment, health, and safety (research, etc.)
NCI	National Cancer Institute (NIH)
NCL	Nanotechnology Characterization Laboratory (NIH)
NCN	Network for Computational Nanotechnology (NSF)
NCNR	NIST Center for Neutron Research
NCTR	National Center for Toxicological Research (FDA)
NE	[Office of] Nuclear Energy (DOE)
NEHI	Nanotechnology Environmental and Health Implications (Working Group)
NHLBI	National Heart, Lung, and Blood Institute (NIH)
NIAID	National Institute of Allergy and Infectious Diseases (NIH)
NIBIB	National Institute of Biomedical Imaging and Bioengineering (NIH)
NIEHS	National Institute of Environmental Health Sciences (NIH)
NNCI	National Nanotechnology Coordinated Infrastructure (NSF)
NNCO	National Nanotechnology Coordination Office
NNI	National Nanotechnology Initiative
NRL	Naval Research Laboratory
NS&E	nanoscale science and engineering
NSET	Nanoscale Science, Engineering, and Technology Subcommittee of the NSTC
NSLS-II	National Synchrotron Light Source II
NSRC	Nanoscale Science Research Center (DOE)
NSTC	National Science and Technology Council
OECD	Organisation for Economic Co-operation and Development

[1] See Table 1, p. 2, for abbreviations of NNI participating agencies not spelled out in this list.

OMB Office of Management and Budget (Executive Office of the President)

ONR Office of Naval Research

ORD Office of Research and Development (EPA)

OSTP Office of Science and Technology Policy (Executive Office of the President)

PCA Program Component Area of the National Nanotechnology Initiative

RNA ribonucleic acid

RF radio frequency

RSV respiratory syncytial virus

R&D research and development

SBIR Small Business Innovation Research program

STC Science and Technology Center (NSF)

STM scanning tunneling microscopy

STEM science, technology, engineering, and mathematics

STTR Small Business Technology Transfer Research program

Executive Summary

The President's 2023 Budget requests $1.99 billion for the National Nanotechnology Initiative (NNI), cumulatively totaling over $40.7 billion since the inception of the NNI in 2001[2] (including the 2023 request). This highest-ever request reflects the continued importance of investments that advance the fundamental understanding of and ability to control matter at the nanoscale, as well as the translation of that knowledge into technological breakthroughs that benefit society. Past research has led to applications in areas as diverse as clean energy, water purification, consumer electronics, textiles, aerospace, automotive, infrastructure, agriculture, and medicine.

As highlighted in the research and development examples provided in this report, nanotechnology has become a broadly enabling technology and underpins technologies of the future such as quantum information science, artificial intelligence, biotechnology, and advanced manufacturing and computing. NNI investments in foundational nanotechnology research, electronic devices and systems, research infrastructure, and education provide a strong foundation for, and are synergistic with, the efforts to renew U.S. leadership in the semiconductor and microelectronics industries funded and authorized under the CHIPS and Science Act of 2022 (Public Law 117-167). Furthermore, as evidenced throughout the Covid-19 pandemic, nanotechnology has the potential to help address the biggest challenges facing the world. For example, in addition to pandemic preparedness, nanotechnology will play a role in combating climate change, providing food safety and abundance, delivering green energy technologies, and ensuring access to clean water.

The NNI investments in 2021 and 2022 and those proposed in 2023 reflect a sustained emphasis on broad, fundamental research in nanoscience. Through this sustained support, the President's Budget includes nanotechnology investments that will further the progress of the NNI to advance a world-class research portfolio, facilitate commercialization of nanotechnology-enabled applications, support a dynamic infrastructure and skilled workforce, and ensure responsible development of nanotechnology.

This document serves as the annual report for the National Nanotechnology Initiative called for under the provisions of the 21st Century Nanotechnology Research and Development Act (15 USC §7501). The report also addresses the requirement for Department of Defense reporting on its nanotechnology investments (10 USC §2358).

2 References to years in this report are to fiscal years unless otherwise noted.

What is Nanotechnology?

Nanotechnology encompasses science, engineering, and technology at the nanoscale, which is about 1 to 100 nanometers. (A nanometer is one-billionth of a meter.) Nanoscale materials can behave differently than the same bulk material. For example, a material's melting point, color, strength, chemical reactivity, and more may change at the nanoscale.

Nanotechnology has broad application across many sectors and underpins areas such as artificial intelligence, quantum information science, and advanced manufacturing. Nanotechnology innovations are ensuring continued U.S. leadership in the semiconductor and strategic computing industries and advancement in many other national priorities, including space exploration, energy, medicine, agriculture, and national security.

Examples of nanotechnology innovations are illustrated below: (a) quantum hardware fabricated using nanomechanical resonators made of lithium niobate; (b) a lipid nanoparticle, which facilitates delivery of messenger RNA (mRNA) in COVID-19 vaccines and many other pharmaceuticals; (c) a silicon nanowire that is shaped at near-atomic scale using a novel electron beam nanofabrication technique; (d) a grease-proof and water-resistant disposable food container made of recyclable cellulose nanocomposites; (e) a graphene oxide foam that filters uranium and other heavy metals from water; (f) a graphene-based electronic tattoo that provides continuous mobile monitoring of blood pressure; and (g) a gas sensor that mimics the sensitivity and selectivity of a human nose using nanoengineered materials.

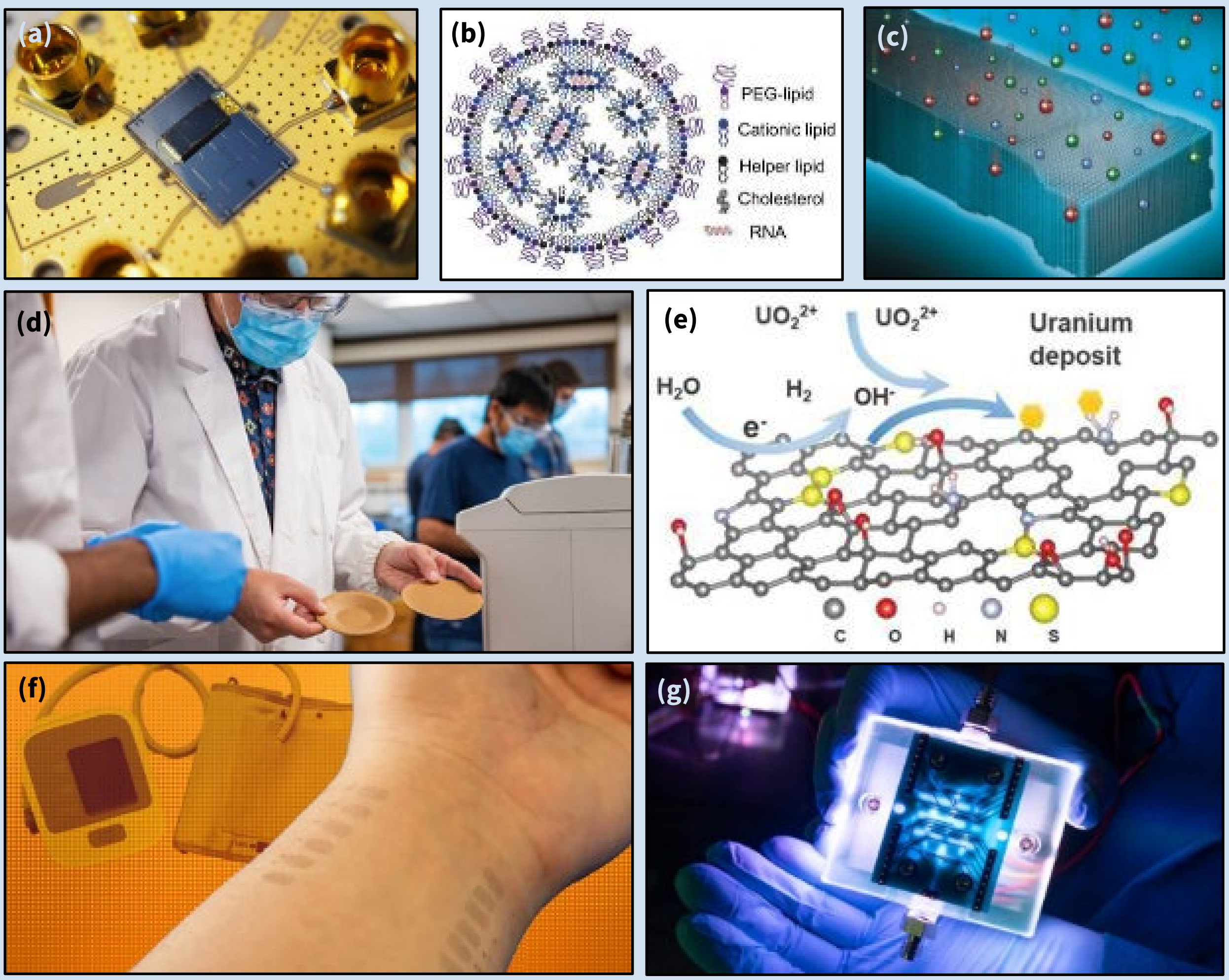

Image credits: (a) Stanford University; (b) *Small Methods* (Wiley); (c) Brookhaven National Laboratory, reproduced with permission from Wiley-VCH; (d) University of Maine; (e) Massachusetts Institute of Technology; (f) University of Texas at Austin; (g) University of Notre Dame. For more information on nanotechnology benefits and applications, please visit https://www.nano.gov/about-nanotechnology/applications-nanotechnology.

1. Introduction

The National Nanotechnology Initiative (NNI) is a U.S. Government research and development (R&D) initiative. Twenty Federal departments, independent agencies, and commissions work together toward the shared vision of *a future in which the ability to understand and control matter at the nanoscale leads to ongoing revolutions in technology and industry that benefit society*. The NNI supports a shared infrastructure and establishes shared goals, priorities, and strategies to enhance interagency coordination of nanotechnology R&D that builds on agency-specific missions and activities, and leverages resources while avoiding duplication. Table 1 lists the agencies currently participating in the NNI. More information about the structure, goals, and priorities of the NNI can be found on Nano.gov.

The ability to understand and control matter at the nanoscale enables unique physical, chemical, and biological properties with broad applications across disciplines and industrial sectors. Past research has enabled current nanotechnology-enabled applications in areas as diverse as clean energy, water purification, consumer electronics, textiles, aerospace, automotive, infrastructure, agriculture, and medicine. The nanotechnology research underway today, and the ongoing NNI investments in research infrastructure and education, will enable entirely new capabilities and products and help address world challenges such as the climate crisis, food security, clean water, and future pandemics, and will help to renew U.S. leadership in critical industries such as semiconductors and microelectronics.

The NNI participating agencies work together to advance discovery and innovation across the entire nanotechnology R&D enterprise. The NNI portfolio ranges from early-stage fundamental science to applications-driven research and encompasses activities embedded in many diverse fields of science and technology. The NNI brings together representatives from multiple agencies to leverage knowledge and resources based on their respective roles and responsibilities. The NNI engages the broader nanotechnology R&D community, including academia and the private sector as appropriate to promote technology transfer and facilitate commercialization. The development of strategic collaborations, including public-private-nonprofit partnerships, helps to strengthen and advance key areas within the nanotechnology ecosystem. In addition to R&D efforts, the NNI agencies are working together to build the nanotechnology workforce of the future, with efforts aimed across the spectrum from K-12 through postgraduate research training, including activities to broaden participation in nanoscale science and education, in keeping with the provisions of the CHIPS and Science Act of 2022 (Public Law 117-167).

The NNI benefits from engagement with a broad range of stakeholder groups, including allies and partners with shared values. Nanotechnology remains an area of intense R&D activity worldwide. The National Nanotechnology Coordination Office (NNCO) and NNI agencies engage with international regulatory and research agencies and nanotechnology associations from around the world to share best practices, explore opportunities for collaboration, and promote science-based regulation.

This document highlights significant progress toward the five goals identified in the 2021 NNI Strategic Plan.[3] Chapter 2 of this report presents budget information and highlights of agency plans and priorities by Program Component Area (PCA).[4] Chapter 3 includes examples of progress toward the NNI goals. Contact information for agency representatives to the Nanoscale Science, Engineering, and Technology (NSET) Subcommittee of the National Science and Technology Council and for NNCO staff is provided in Appendix A.

3 https://www.nano.gov/sites/default/files/pub_resource/NNI-2021-Strategic-Plan.pdf

4 PCA definitions are posted on Nano.gov at https://www.nano.gov/pcadefinitions.

Table 1: Federal Departments and Agencies Participating in the NNI
Consumer Product Safety Commission (CPSC)*†
Department of Agriculture (USDA)
Agricultural Research Service (ARS)*
Forest Service (FS)*
National Institute of Food and Agriculture (NIFA)*
Department of Commerce (DOC)
Bureau of Industry and Security (BIS)
Economic Development Administration (EDA)
International Trade Administration (ITA)
National Institute of Standards and Technology (NIST)*
Patent and Trademark Office (USPTO)
Department of Defense (DOD)*
Department of Education (ED)
Department of Energy (DOE)*
Department of Health and Human Services (HHS)
Agency for Toxic Substances and Disease Registry (ATSDR)
Biomedical Advanced Research and Development Authority (BARDA)*
Food and Drug Administration (FDA)*
National Center for Environmental Health (NCEH)
National Institute for Occupational Safety and Health (NIOSH)*
National Institutes of Health (NIH)*
Department of Homeland Security (DHS)
Department of the Interior (DOI)
Bureau of Reclamation (USBR)*
Bureau of Safety and Environmental Enforcement (BSEE)*
Geological Survey (USGS)
Department of Justice (DOJ)
National Institute of Justice (NIJ)*
Department of Labor (DOL)
Occupational Safety and Health Administration (OSHA)
Department of State (State)
Department of Transportation (DOT)
Federal Highway Administration (FHWA)*
Department of the Treasury (Treasury)
Environmental Protection Agency (EPA)*
Intelligence Community (IC)
International Trade Commission (USITC)†
National Aeronautics and Space Administration (NASA)*
National Science Foundation (NSF)*
Nuclear Regulatory Commission (NRC)†

* Denotes agencies (or organizations within agencies) reporting funding for nanotechnology R&D in Table 5 below

† Denotes an independent commission that is represented on NSET but is non-voting

2. NNI Budget and Program Plans

Budget Summary

The President's 2023 Budget requests $1.99 billion for the NNI, with a continued investment in the foundational research that will fuel new discoveries and application-driven research and development to advance technologies of the future and address world challenges. Cumulatively totaling over $40.7 billion (including the 2023 request), NNI investments support research to understand matter at the nanoscale and to translate this knowledge into technological breakthroughs that benefit all Americans. The NNI investments in 2021 and 2022 and those proposed for 2023 reflect a sustained emphasis on fundamental research in nanoscience; research to advance applications, devices, and systems; and support for the responsible development of nanotechnology. The NNI budget represents the sum of the nanotechnology-related investments allocated by each of the participating agencies (the "NNI crosscut"). Each agency determines its budget for nanotechnology R&D in coordination with the Office of Management and Budget (OMB), the Office of Science and Technology Policy (OSTP), and Congress. NNI agencies collaborate closely—facilitated through the NSET Subcommittee; its working group, communities of interest, coordinators, and strategic liaisons; and the NNCO—to create an integrated R&D program that leverages and amplifies resources and efforts to advance NNI goals and meet individual agency mission needs and objectives. NNI agencies support significant investments in research infrastructure, developing new research tools, and making these tools available through user facilities. The NNI also supports science, technology, engineering, and mathematics (STEM) education to prepare the workforce of the future.

This document reports agency investments using existing appropriations as well as supplemental funding to address the COVID-19 pandemic, including major supplemental funding in both 2021 and 2022 by the Biomedical Advanced Research and Development Authority. Agencies are funding a variety of research and development activities as part of this effort, including many that utilize nanotechnology to detect, treat, and prevent the disease; and to understand the SARS-CoV-2 virus and how it spreads.

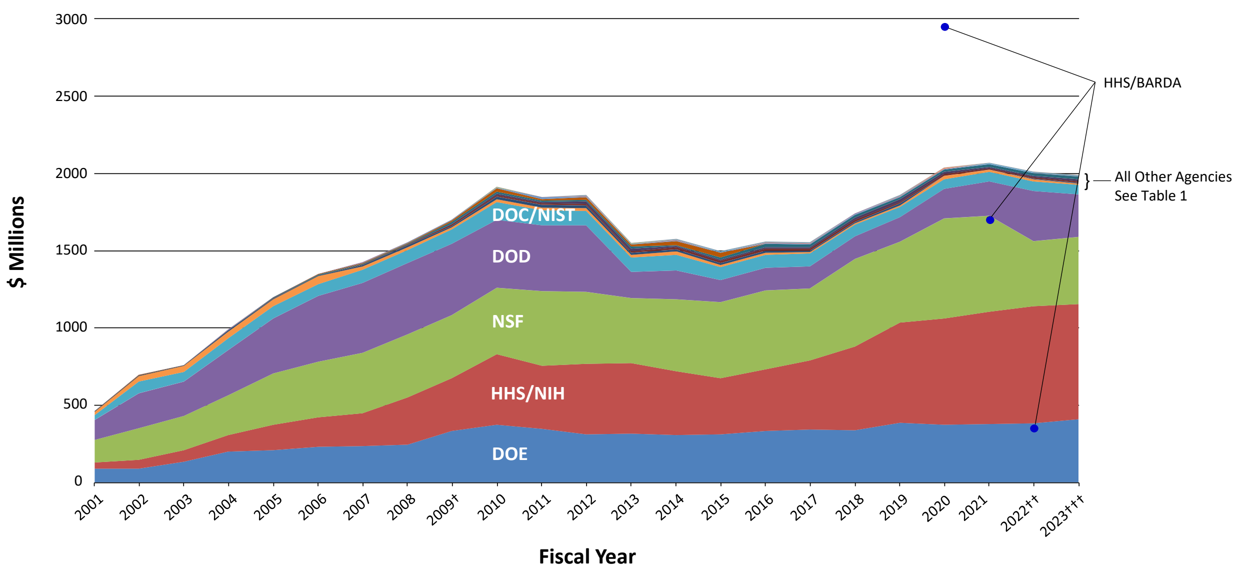

Figure 1. NNI Funding by Agency, 2001–2023.*

* 2021 figures include supplemental funding. BARDA investments (blue dots) not included in line graph totals.

† 2009 figures do not include American Recovery and Reinvestment Act funds for DOE, NSF, NIH, and NIST.

†† 2022 numbers are based on appropriated levels.

††† 2023 Budget.

Table 2: Actual 2021 Agency Investments by Program Component Area
(dollars in millions)

Agency	1. Foundational Research	2. Nanotechnology-Enabled Applications, Devices, and Systems	3. Research Infrastructure and Instrumentation	4. Education and Workforce Development	5. Responsible Development	NNI Total
CPSC	0.0	0.0	0.0	0.0	0.4	0.4
DOC/NIST	15.5	10.1	33.0	0.0	4.1	62.7
DOD	144.0	55.9	16.5	0.8	1.2	218.3
DOE	181.7	55.2	140.8	0.0	0.0	377.7
DOI/USBR	0.3	0.0	0.0	0.0	0.0	0.3
DOJ/NIJ	0.5	0.4	0.0	0.0	0.0	0.9
DOT/FHWA	0.0	0.2	0.0	0.0	0.0	0.2
EPA	0.0	0.0	0.0	0.0	2.5	2.5
HHS (total)	260.8	2138.4	27.4	0.0	30.6	2457.2
BARDA*	0.0	1708.8	0.0	0.0	0.0	1708.8
FDA	0.0	0.0	0.0	0.0	10.0	10.0
NIH**	260.8	429.6	27.4	0.0	11.5	729.3
NIOSH	0.0	0.0	0.0	0.0	9.1	9.1
NASA	0.0	12.6	0.0	0.0	0.0	12.6
NSF* **	393.2	109.7	30.4	25.2	62.2	620.7
USDA (total)	5.0	15.5	1.0	0.1	1.8	23.4
ARS	0.0	4.0	0.0	0.0	0.0	4.0
FS	0.5	3.1	0.2	0.0	0.0	3.7
NIFA	4.6	8.3	0.8	0.1	1.8	15.7
TOTAL†	**1000.9**	**2397.9**	**249.1**	**26.1**	**102.8**	**3776.9**

* All of BARDA's 2021 investment is in supplemental funding. $1.5 billion previously reported by BARDA as 2021 investments (in the NNI Supplement to the President's 2022 Budget) were re-categorized as 2020 supplemental investments.

** NIH totals include $17.9 million in supplemental 2021 funding (PCA 1 $9.7 million; PCA 2 $7.1 million, PCA 3 $1.1 million).

*** NSF totals include $9 million in supplemental 2021 funding (PCA 1 $6.83 million; PCA 2 $0.17 million; PCA 4 $2.0 million).

† In Tables 2–6, totals may not add, due to rounding.

The President's 2023 Budget supports nanoscale science, engineering, and technology R&D at 11 agencies. The five Federal organizations with the largest proposed 2023 investments (representing 96% of the NNI total) are:

- HHS/NIH (nanotechnology-based biomedical research at the intersection of life and physical sciences).
- NSF (fundamental research and education across all disciplines of science and engineering).
- DOE (fundamental and applied research providing a basis for new and improved energy technologies).
- DOD (science and engineering research advancing defense and dual-use capabilities).
- DOC/NIST (fundamental research and development of measurement and fabrication tools, analytical methodologies, metrology, and standards for nanotechnology).

Table 3: Estimated 2022 Agency Investments by Program Component Area
(dollars in millions)*

Agency	PCA 1.	PCA 2.	PCA 3.	PCA 4.	PCA 5.	Total
CPSC	0.0	0.0	0.0	0.0	0.4	0.4
DOC/NIST	15.4	9.6	32.9	0.0	4.3	62.2
DOD	163.7	59.1	98.2	1.3	1.2	323.5
DOE	182.2	53.7	149.1	0.0	0.0	385.0
DOI/BSEE	0.0	0.5	0.0	0.0	0.0	0.5
DOI/USBR	0.3	0.0	0.0	0.0	0.0	0.3
DOJ/NIJ	0.5	1.0	0.0	0.0	0.0	1.5
DOT/FHWA	0.0	0.2	0.0	0.0	0.0	0.2
EPA	0.0	0.0	0.0	0.0	4.1	4.1
HHS (total)	264.4	802.1	27.7	0.0	30.6	1124.8
BARDA**	0.0	352.1	0.0	0.0	0.0	352.1
FDA	0.0	0.0	0.0	0.0	9.6	9.6
NIH***	264.4	450.0	27.7	0.0	11.9	754.0
NIOSH	0.0	0.0	0.0	0.0	9.2	9.2
NASA	0.0	13.2	0.0	0.0	0.0	13.2
NSF	289.3	79.5	22.3	19.0	14.5	424.5
USDA (total)	4.9	14.5	1.3	0.1	1.8	22.6
ARS	0.0	4.0	0.0	0.0	0.0	4.0
FS	0.3	2.1	0.5	0.0	0.0	2.9
NIFA	4.6	8.3	0.8	0.1	1.8	15.7
TOTAL	**920.7**	**1033.3**	**331.5**	**20.4**	**56.9**	**2362.7**

Table 4: Proposed 2023 Agency Investments by Program Component Area
(dollars in millions)

Agency	PCA 1.	PCA 2.	PCA 3.	PCA 4.	PCA 5.	Total
CPSC	0.0	0.0	0.0	0.0	1.2	1.2
DOC/NIST	15.7	9.5	31.5	0.0	4.3	61.0
DOD	156.5	50.6	66.9	1.4	1.2	276.7
DOE	195.8	72.2	141.7	0.0	0.0	409.7
DOJ/NIJ	0.5	1.0	0.0	0.2	0.0	1.7
DOT/FHWA	0.0	0.5	0.0	0.0	0.0	0.5
EPA	0.0	0.0	0.0	0.0	2.7	2.7
HHS (total)	265.8	441.3	26.8	0.0	32.6	766.5
FDA	0.0	0.0	0.0	0.0	10.8	10.8
NIH	265.8	441.3	26.8	0.0	12.6	746.5
NIOSH	0.0	0.0	0.0	0.0	9.2	9.2
NASA	0.0	10.4	0.0	0.0	0.0	10.4
NSF	261.3	101.0	26.7	21.5	21.9	432.3
USDA (total)	5.9	16.4	1.6	0.1	2.2	26.2
ARS	0.0	4.0	0.0	0.0	0.0	4.0
FS	0.3	2.3	0.6	0.0	0.0	3.2
NIFA	5.6	10.1	1.0	0.1	2.2	19.0
TOTAL	**901.5**	**702.9**	**295.1**	**23.2**	**66.1**	**1988.8**

* Headings in Tables 3 and 4 are abbreviated to PCA numbers.
** BARDA total includes $350 million in 2022 supplemental funding.
*** NIH totals include $9.2 million in supplemental 2022 funding (PCA 1 $0.6 million; PCA 2 $8.5 million, PCA 3 $0.1 million).

Table 5: NNI Budget, by Agency, 2021–2023
(dollars in millions)

Agency	2021 Actual	2022 Estimated*	2023 Proposed
CPSC	0.4	0.4	1.2
DOC/NIST	62.7	62.2	61.0
DOD**	218.3	323.5	276.7
DOE***	377.7	385.0	409.7
DOI/BSEE	0.0	0.5	0.0
DOI/USBR	0.3	0.3	0.0
DOJ/NIJ	0.9	1.5	1.7
DOT/FHWA	0.2	0.2	0.5
EPA	2.5	4.1	2.7
HHS (total)	2457.2	1124.8	766.5
BARDA	1708.8	352.1	0.0
FDA	10.0	9.6	10.8
NIH	729.3	754.0	746.5
NIOSH	9.1	9.2	9.2
NASA	12.6	13.2	10.4
NSF	620.7	424.5	432.3
USDA (total)	23.4	22.6	26.2
ARS	4.0	4.0	4.0
FS	3.7	2.9	3.2
NIFA	15.7	15.7	19.0
TOTAL	**3776.9**	**2362.7**	**1988.8**

* 2022 numbers are based on appropriated levels.

** Funding levels for DOD include the combined budgets of the Air Force, Army, Navy, Defense Advanced Research Projects Agency, Defense Threat Reduction Agency, Office of the Under Secretary of Defense for Research and Engineering, and Joint Program Executive Office for Chemical, Biological, Radiological, and Nuclear Defense.

*** Funding levels for DOE include the combined budgets of the Office of Science, Office of Energy Efficiency and Renewable Energy, Office of Nuclear Energy, and Office of Fossil Energy and Carbon Management.

A significant proportion of agencies' nanotechnology investments typically come from "core" R&D programs, which makes it difficult to predict the number of and success rate of nanotechnology-related proposals. As a result, the actual investments reported are often higher than the previously published estimates or proposed values. For example, the actual NNI investment for 2021 (nearly $3.8 billion, including $1.7 billion from BARDA for COVID diagnostics and vaccine research) is much higher than the 2021 requested value published in the NNI Supplement to the President's 2021 Budget ($1.7 billion).

The proposed 2023 NNI investments outlined in this report are synergistic with efforts to renew U.S. leadership in the semiconductor and microelectronics industries funded and authorized under the CHIPS and Science Act of 2022 (Public Law 117-167). Foundational nanotechnology research (PCA 1) and nanoelectronic devices and systems (PCA 2) will provide leapfrog capabilities in microelectronics. Research centers and user facilities (PCA 3) supported by the NNI participating agencies DOE, DOD, NSF, and NIST include an extensive network of cleanrooms and other nanofabrication and characterization capabilities that are a strong foundation for the additional microelectronics infrastructure to be developed with CHIPS Act funding. NSF will build on its existing nanoscience and engineering education programs (PCA 4) to develop the semiconductor workforce and education activities funded under the CHIPS Act.

Programmatic Plans and Changes by PCA

The budget details in this document represent NNI agency support for a vast array of nanotechnology R&D activities across scientific disciplines, application areas, and technology maturity levels. This section provides highlights of agency plans relating to each of the NNI Program Component Areas for 2023. The PCAs are aligned with the goals in the 2021 NNI Strategic Plan. PCA definitions[5] and additional details and examples can be found on Nano.gov.

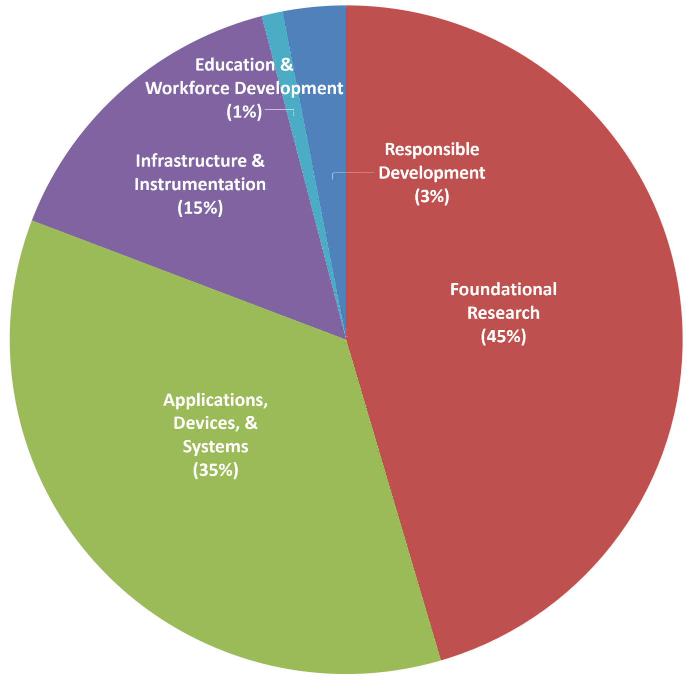

Figure 2. Breakout of NNI Funding by Program Component Area in the 2023 Budget.

PCA 1. Foundational Research

Foundational research continues to be the largest area of investment, accounting for 45% of the proposed NNI total for 2023. NIH and NSF are the largest contributors to this PCA, followed by DOE and DOD. NSF, DOD, and DOE invest 60%, 57%, and 48% of their totals, respectively, in this category. The investment by NNI agencies in foundational research helps to ensure new discoveries that fuel the innovations of the future.

While most of NSF's research in PCA 1 is supported with individual and small group research grants from across NSF directorates, a subset of Engineering Research Centers (ERCs), Science and Technology Centers (STCs), Centers for Chemical Research, Industry-University Cooperative Research Centers (IUCRCs), and other centers programs support various aspects of nanoscale science and engineering (NS&E). For example, about 60 percent of the Materials Research Science and Engineering Centers (MRSECs) pursue NS&E-related fundamental research.

NSF invests in understanding the nanoscale machines that make up the nucleus of a cell and control cell function through its Understanding the Rules of Life: Epigenetics,[6] and Physics Frontiers Centers[7] programs, and through core programs in the Molecular and Cellular Biosciences (MCB) and Chemistry divisions. NSF is expanding its efforts in nanobiotechnology associated with synthetic biology and synthetic cells through the Designing Synthetic Cells Beyond the Bounds of Evolution solicitation;[8] a Dear Colleague Letter, Sentinel Cells for Surveillance and Response to Emergent Infectious Diseases;[9] and through core programs in the MCB Division within the Directorate for Biological Sciences (BIO) and in the Chemical, Bioengineering, Environmental and Transport Systems (CBET) Division within the Directorate for Engineering (ENG).

5 https://www.nano.gov/pcadefinitions
6 https://www.nsf.gov/pubs/2020/nsf20512/nsf20512.htm
7 https://www.nsf.gov/mps/phy/pfc_program.jsp
8 https://www.nsf.gov/pubs/2021/nsf21531/nsf21531.htm
9 https://www.nsf.gov/pubs/2020/nsf20105/nsf20105.jsp

NSF's PCA 1 investments also include foundational research on sustainable nanomanufacturing, nanoelectronics (including semiconductors and future computing paradigms), nanosensors, and water sustainability. Special emphasis will be in several areas, including developing foundational concepts for new nanomanufacturing methods at confluence with digitization, biotechnology, artificial intelligence (AI), and cognitive sciences, including solicitations on Designing Synthetic Cells Beyond the Bounds of Evolution[10] and Reproducible Cells and Organoids via Directed-Differentiation Encoding (RECODE)[11] that will lead to scalable and reproducible cell and organ production for biomanufacturing and biomedicine applications. Other areas of emphasis will include discovering and using novel nanoscale fabrication processes and innovative concepts to produce revolutionary materials, devices, systems, and architectures to advance the field of electronics beyond Moore's Law, including "Brain-like Computing" and "Intelligent Cognitive Assistants" research, as well as efforts in sensors and water. Focus areas will include the use of nanotechnology and nanoscale materials to build more sensitive, specific, and adaptable sensors, and the development of new sensors to detect engineered nanomaterials across their life cycles to assess their potential impacts, including the Biosensing[12] and Biophotonics[13] programs in the CBET Division. Research will also focus on taking advantage of the unique properties of engineered nanomaterials and systems to increase water availability, improve the efficiency of water delivery, and enable next-generation water monitoring systems.

NIH advances creative, fundamental nanoscience discoveries to ultimately enhance health, lengthen life, and reduce illness and disability through a variety of mechanisms and approaches. The NIH nanotechnology investment portfolio supports basic research primarily through grants funded by many of the NIH institutes and centers. Current research efforts focus on fundamental research that will advance new medical diagnostics, therapeutics, and vaccines based on nanotechnologies. Due to the successful integration of nanotechnology-based R&D into numerous biomedical applications, scientists can propose ideas via broad funding opportunity announcements supported by a large number of NIH institutes, centers, and offices.

The National Cancer Institute (NCI) at NIH supports basic, applied, and translational research in the area of cancer nanotechnology. In particular, the funding opportunity PAR-20-284, Innovative Research in Cancer Nanotechnology (IRCN),[14] covers mechanistic studies contributing to fundamental understanding of nanoparticle design rules and mechanisms behind their *in vivo* interactions. NIH/NCI supports a breadth of research activities that utilize nanotechnology to address cancer in both diagnostic and therapeutic areas. Among diagnostic research highlights, NCI-funded researchers are working on high-throughput nanoplasmonic exosome testing (NEXT) of immunotherapies, continue to develop pH transistor nanoprobes for detection of metastasis, and have worked on nanoscale and biomolecular engineered technologies for neoantigen-specific T cell capture and characterization. Nanotechnology applications in immunotherapy continue to accelerate. For example, research funded by NCI includes development of nano-optogenetic immunotherapy for B cell lymphoma, development of "nanosacs" for systemic delivery of small interfering ribonucleic acid (siRNA) for checkpoint blockade immunotherapy of head and neck squamous cell cancer, use of macrophage reprogramming messenger RNA (mRNA) nanocarriers for initial clinical testing in cancer, and translation of nanoscale metal-organic frameworks for radiotherapy-radiodynamic therapy treatment of head and neck cancer.

10 https://www.nsf.gov/pubs/2021/nsf21531/nsf21531.htm
11 https://www.nsf.gov/pubs/2021/nsf21608/nsf21608.htm
12 https://beta.nsf.gov/funding/opportunities/biosensing-0
13 https://beta.nsf.gov/funding/opportunities/biophotonics-1
14 https://grants.nih.gov/grants/guide/pa-files/par-20-284.html

The NIH National Institute of Allergy and Infectious Diseases (NIAID) supports foundational research on the use of nanotechnology to prevent and treat a wide spectrum of immunologic and infectious diseases. Multiple human immunodeficiency virus (HIV) vaccine basic research and development programs in the NIAID Division of AIDS support nanoparticle technology, including for example, protein nanoparticle and mRNA packaged into lipid nanoparticle (LNP) platforms being evaluated both *in vitro* and in appropriate animal models. These programs include: the HIV Vaccine Research and Design (HIVRAD) program, the Innovation for HIV Vaccine Discovery (IHVD) program, the Consortia for HIV/AIDS Vaccine Development (CHAVD) program, the Consortium for Innovative AIDS Research in Nonhuman Primates (CIAR-NHP) program, the Simian Vaccine Evaluation Units (SVEUs), and the Integrated Preclinical/Clinical AIDS Vaccine Development program (IPCAVD). Other ongoing NIAID-funded nanotechnology projects falling under PCA 1 include nanoscale reconstruction of mechanical systems involved in disease pathogenesis; development of a scalable, drug-combination nano-platform technology called DcNPs (drug combination nanoparticles) that enables the stabilizing of insoluble and soluble short-acting antiretroviral drugs together in an injectable suspension for long-acting therapy for children with HIV; use of nano-flow liquid chromatography coupled to selected reaction monitoring mass spectrometry to quantify protein levels in signaling networks in the immune system; development of nanoparticles that interact with inflammatory cells and reprogram them to reduce the pathologic inflammatory response; discovery and development of nanoparticle-based vaccine adjuvants to enhance vaccine efficacy and durability; and novel dendrimer-nanodevices conjugated to drugs to target activated microglia and attenuate the neurologic injury due to central nervous system tuberculosis.

NIH's National Institute of Dental and Craniofacial Research (NIDCR) continues strategic investments in nanotechnology-based initiatives leveraging the promise of nanotechnology as a 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. NIDCR continues to participate in the National Academies Forum on Regenerative Medicine, which organized a recent workshop and publication[15] covering nanotechnology-based tools for precise manipulation of the immune system for regenerative medicine. NIDCR will continue its support for the Dental, Oral and Craniofacial Tissue Regeneration Consortium (DOCTRC) through 2025.[16]

The DOE Office of Basic Energy Sciences (BES) supports fundamental nanoscience research in the fields of materials science, chemical science, geoscience, and bioscience, with the goal of understanding, predicting, and ultimately controlling matter and energy at the level of electrons, atoms, and molecules. This basic research is performed primarily at universities and DOE national laboratories through single-PI and small group projects. In addition, BES supports nanoscience as part of larger activities such as Energy Frontier Research Centers and Energy Innovation Hubs, with an emphasis on use-inspired basic research, in coordination with DOE technology programs to ensure translation of basic science to applied research and development. These investments will continue in 2023, with a particular focus on foundational research to underpin clean energy technologies and advanced manufacturing.

DOD recognizes the importance of nanotechnology and nanomaterials to the ongoing modernization of the current force, and also recognizes the revolutionary changes that these technologies may bring to future warfighting capabilities. The department is committed to maintaining a broad base of

15 https://doi.org/10.17226/26551

16 https://doctrc.org/; accessed 8/1/22. See also NNI Supplement to the Presidents 2022 Budget, pp. 9, 40: https://www.nano.gov/sites/default/files/pub_resource/NNI-FY22-Budget-Supplement.pdf.

foundational nanoscience research across the department's laboratories, and will continue to collaborate with other Federal agencies in this arena.

The Naval Research Laboratory (NRL) efforts in foundational research cover three main areas: materials/assembly, interactions, and nanosystems. In the area of materials/assembly, NRL is developing novel nanoscale materials through a combination of nanofabrication, growth, and directed chemical and biological assembly. Structures include both inorganic and bio/inorganic hybrids. The area of Interactions investigates the basic properties of nanostructures and how these materials interact with their environment. The goal of the nanosystems area is to develop functional systems of interacting nanomaterials. Examples of such nanosystems include entangled quantum dots, interacting nanophotonic systems, and bio/inorganic artificial enzymes.

The Office of Naval Research (ONR) supports bionanotechnology research with emphases on fabrication techniques for hierarchical, biologically based materials with defined properties; DNA nanotechnology and application for functional device platforms; synthesis and patterning of materials by microorganisms; and design and fabrication of bio-inspired and biomimetic materials and devices using Nature's design principles. ONR also supports programs to investigate the scientific phenomena that define the unique properties of structural and multifunctional nanomaterials. A special emphasis is on identifying material systems and processes enabling the assembly of these materials at mesoscale and beyond while preserving and potentially enhancing the material properties, initially defined at the nanoscale. The ONR Nanoelectronics program fosters and encourages high-risk innovative research in nanoscience that will enable revolutionary new electronic devices with a plausible route to either classical information processing with size/weight/power and/or computational speed/algorithmic advantages over state-of-the-art, or robust quantum information processing in solid-state circuits. Research challenges include identifying fundamental building blocks of classical information handling beyond transistors; novel "topologically protected" qubit designs for quantum computing in decohering environments; alternative computing architectures that circumvent the von Neumann memory-compute information bottleneck; and reliable and cost-effective means to synthesize and fabricate electronic circuitry at the ultimate limits of spatial resolution, including schemes to grow, stabilize, and utilize novel two-dimensional (2D) electronic materials. In 2023, ONR will launch another Multidisciplinary University Research Initiative (MURI) topic, Supremacy over Quantum: Efficient Real-World Optimization on Stochastic Binary Networks, focused on probabilistic computing using hardware-accelerated true random bit generation from transport fluctuations in nanoscale devices.

The Army Engineer Research and Development Center (ERDC) is conducting basic research on adjusting quantum materials by gating of quantum spin liquids (QSLs) using ionic liquids. One study is focused on how ionic liquids can be tuned to interact with the surface of alpha-$RuCl_3$ as a candidate QSL material to form a gate, making a more fault-tolerant quantum material.

Planned research at the Army's Institute for Soldier Nanotechnologies (ISN) emphasizes exploration of novel phenomena associated with fundamental processes (physical, chemical, biological) at the nanoscale or arising from nanostructural features in materials and devices, recognizing that nanotechnology entails much more than making materials that are very small and have very low weight. ISN basic research supports each of the six priorities of the new Army Futures Command.[17] This includes 14 projects within three Strategic Research Areas (SRAs): SRA-1, Soldier Protection, Battlefield Care (including injectable nanoparticles for rapid hemostasis in treatment of wounds) and Sensing;

[17] https://armyfuturescommand.com/cft/

SRA-2, Augmenting Situational Awareness; and SRA-3, Transformational Nano-optoelectronic Soldier Capabilities.

University researchers supported by the Army Research Office (ARO) are developing a new computational model for fabricating segregation-stabilized nanocrystalline alloys that utilize a solute as a means to keep the individual crystals (grains) of the material at the nanoscale. This research will lay a technical foundation for designing nanocrystalline alloys that employ alloy segregation for potential protective and hypersonic applications.

The Defense Advanced Research Projects Agency (DARPA) Molecular Systems and Materials Assembly program is supporting research on the morphology of nanoscale interfaces and the role of local energy gradients to sense and restore morphology and function, to better understand how to design materials that can self-regulate their morphology, potentially leading to enhanced persistence in solid-state batteries and corrosion prevention technologies. Under the DARPA Electronics Resurgence Initiative (ERI), the Joint University Microelectronics Program (JUMP) 2.0 will investigate foundational materials and device technologies for electronics.

NIST's foundational nanotechnology research portfolio includes the development of cutting-edge approaches to design and accurately measure the size, shape, quantity, and physico-chemical complexity of nanoparticles, nanostructured films, and nanocomposites in a variety of environments. For example, NIST researchers are studying the impact of UV exposure and outdoor weathering on the scratch resistance of coatings using a NIST-developed nanoscratch test to simulate scratch and other mechanisms of coating damage. The test will also be applied to UV-exposed photovoltaic backsheet and other polymer composites to investigate interfacial properties of multilayer, multicomponent systems.

Optical metasurface technologies that enable optical control in thin, easily manufactured elements that can replace traditional optics in many applications are being advanced by NIST. New capabilities in photonic interfaces to atomic-scale quantum systems are advancing national priorities in precision time keeping and quantum technologies. Metasurfaces also enable new applications in ultrafast and nonlinear optics, as well as advanced imaging and photonic sensing.

NIST is developing best practices and disseminating new measurement methods and data analysis techniques that precisely and accurately determine the thermodynamics of DNA nanostructure assembly. Improved data will inform the creation of predictive models of nucleic acid systems and can also be applied to drug development.

USDA supports foundational R&D in nanotechnology through programs at NIFA and the Forest Service. NIFA supports foundational research in advancing cutting-edge nanoscale science and engineering for solving significant agricultural and food system challenges. The scope of investigation includes discovery and characterization of novel nanoscale phenomena, processes, and properties that are relevant to agriculture and food; development of new platforms leading to novel applications; novel utilization and valorization of nanobiomaterials; exploitation of bio-nano interfaces; and exploration of nanotechnology-related aspects of synthetic biology and additive manufacturing technologies. For example, one project funded in 2020 (and continuing into calendar year 2024) is investigating the use of a non-infectious plant virus nanoparticle for delivery of mRNA into plants, allowing for a temporary change to the behavior of the plants without permanently altering their genetic material. This can allow plants to be temporarily equipped to resist disease, overcome drought conditions, or perform a new function without changing their DNA or creating regulatory hurdles for production.

Nanotechnology research in the Forest Service includes understanding the nanostructure of wood, wood properties, and wood-water interactions with nanotechnology techniques.

PCA 2. Nanotechnology-Enabled Applications, Devices, and Systems

The agencies participating in the NNI support R&D on nanotechnology-enabled devices and systems across many applications, including biomedical innovations to address infectious disease and other health needs, improved infrastructure materials, nanoscale electronics and photonic devices, nanomanufacturing, sensors, and devices and systems for agriculture and space exploration. PCA 2 is the largest category in the NIH NNI investment portfolio, accounting for over 59% of its request.

Several NIH/NCI-funded efforts have an applied focus and are dedicated to developing new and improved diagnostics and therapeutics. The former mostly emphasize high sensitivity and the ability of multiplexed detection. The latter, in addition to nanotechnology-based chemotherapeutics, have gradually migrated to gene therapies and immunotherapies. The newly re-issued PAR-22-071—Toward Translation of Nanotechnology Cancer interventions (TTNCI)[18]—paves the way for late preclinical evaluations, improving entry of nanotechnology cancer interventions to mainstream translational and clinical programs.

Ongoing nanotechnology projects falling under PCA 2 at NIH/NIAID include understanding and correlating the disposition of conserved coronavirus epitopes on subunit vaccines and designed nanoparticles with immunogens, which could lead to triggering different arms of the immune system for a more robust (i.e., broader/universal) immune response to coronavirus antigens within vaccine formulations; and developing an Epstein-Barr virus (EBV) nanoparticle vaccine that is currently in a clinical trial. NIAID is also investigating a variety of nanotechnology-enabled approaches to diagnosis, treatment, and prevention (e.g., vaccines) for malaria; developing a new class of engineered plasmonic nanoparticles to enable screening for lymphatic filariasis; and developing nanotechnology-enabled diagnostics, treatments, and vaccines for giardiasis, hepatitis C, Zika, dengue, rotavirus, enteroviruses, measles, chronic bacterial lung infections, otitis media, respiratory syncytial virus (RSV), and tuberculosis. NIAID also has awarded funding to four academic consortia as part of its efforts to develop pan-beta coronavirus vaccines that could protect against known and unknown SARS-CoV-2 variants as well as coronaviruses with emergence potential.[19]

NIAID is currently supporting the development of several nanoparticle-based vaccine candidates as part of the Institute's priorities to develop a universal influenza vaccine. Many of these vaccine candidates utilize "plug and play" platform technologies that will also be beneficial for rapid response to other emerging viral pathogens.[20] NIAID also supports studies to understand the competency of conserved influenza epitopes displayed on protein nanoparticles and virus-like particles, which could provide platforms that would be optimized for use as immunogens for broad seasonal and universal influenza vaccines.

Projects funded through the NIH Rapid Acceleration of Diagnostics-Radical (RADx-RAD) initiative, overseen by NIDCR and NIH's National Center for Advancing Translational Sciences (NCATS), use nanotechnology and nanomaterial approaches to identify biomarkers in patients with symptomatic and asymptomatic COVID-19.[21] A variety of nanotechnology-based designs are targeting detection of

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[18] https://grants.nih.gov/grants/guide/pa-files/PAR-22-071.html

[19] https://www.nih.gov/news-events/news-releases/niaid-issues-new-awards-fund-pan-coronavirus-vaccines

[20] https://www.niaidcivics.org/

[21] https://grants.nih.gov/grants/guide/rfa-files/RFA-OD-20-020.html, https://grants.nih.gov/grants/guide/rfa-files/RFA-OD-20-021.html

volatile organic compounds emanating from skin and exhaled breath in a passive and noninvasive manner, as well as other oral biosensing technologies targeting SARS-CoV-2 biosignatures sampled from exhaled breath/droplets, saliva, and tissues in the oral cavity. Planning is underway for follow-on funding of these technologies beyond the initial three-year cycle.

NIDCR-supported nanotechnology research includes 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 dental, oral, and craniofacial tissues; and development (in collaboration with NIST) of clinically relevant standards for nanotechnology-based biosensing and dental nanomaterial-based composites including reference materials and quality guidance on research, product development, and upscale manufacturing. NIDCR expects to continue funding targeted biodevice research projects using multiple funding mechanisms such as R01 and R21 funding announcements reissued through 2023.[22] Advanced development and implementation of these novel oral biodevices into integrated detection systems will facilitate incorporation of precision medicine-based approaches into clinical practice. Additionally, due to the shortage of robust diagnostic tests to address the coronavirus pandemic, this biodevice initiative continues to receive increased attention by the scientific community interested in developing biodevices for screening, monitoring, and diagnosis of oral and overall health.

Nanotechnology research supported by NIH's National Institute of Biomedical Imaging and Bioengineering (NIBIB) spans the breadth of biomedicine, including nanoparticles for drug delivery, imaging, diagnostics, and novel forms of therapy. Examples include the use of metal (e.g., gold) nanoparticles in optimizing sensitivity and image resolution of x-ray fluorescence computed tomography and three-dimensional (3D) printing of cell-seeded hydrogel matrices with conducting polymers infused with metal nanoparticles for tissue engineering and neural regeneration. NIBIB also serves as the engineering hub for NIH, developing platform technologies that are then leveraged by disease-specific institutes towards specific patient needs. One key example of this in the nanotechnology space is in the development of ultrathin, lightweight, and stretchable biocompatible nanogenerators that can harvest movement from the human body to power implantable biomedical devices, a technology that is now being leveraged at the National Heart, Lung, and Blood Institute (NHLBI) towards development of self-sustainable intracardiac pacemakers (see sidebar in Goal 1 section below, p. 32).

BARDA helped support the validation and commercialization of lipid nanoparticle mRNA delivery technology through past and current support for Zika and COVID-19 mRNA vaccine development, and will continue to support commercialization of other uses of mRNA technology. Additionally, through its Division of Research, Innovation, and Ventures (DRIVe), BARDA will make investments towards commercializable products utilizing nanotechnologies for new modes of disease detection and diagnostics, including novel biochemical and mechanical sensors that can be used with minimal invasion, e.g., on a wearable device or novel analytical and diagnostic tools designed for at-home use.

The NSF 2023 request for PCA 2 includes funding from core programs in the ENG, Mathematical and Physical Sciences (MPS), and Computer and Information Science and Engineering (CISE) directorates to support development of new principles, design methods, and constructive solutions for nanomaterials and nanodevices. A special focus is on smart, autonomous nanoscale-based devices and systems. The PCA 2 investment also includes applications-, device-, or systems-focused research related to sustainable nanomanufacturing, nanoelectronics (semiconductors and future computing),

[22] https://grants.nih.gov/grants/guide/pa-files/PAR-20-233.html, https://grants.nih.gov/grants/guide/pa-files/PAR-20-232.html

nanosensors, and water sustainability. The NSF IUCRCs conduct nanotechnology research in many of these applications, devices, and systems areas that are of interest to industry partners, where industry provides the majority of the funding.

Sustainable manufacturing includes manufacturing technologies for economical and sustainable integration of nanoscale building blocks into complex, large-scale systems by supporting product, tool, and process design informed by and adhering to the overall constraints of safety, sustainability, and scalability. There will be continued focus on high-performance structural carbon-based nanomaterials, cellulosic nanomaterials, nano-biomanufacturing, and nanomodular systems. The BIO, ENG, and MPS directorates will support engineering biology at the nanoscale for advanced manufacturing activities. The Hierarchical Nanomanufacturing (NanoMFG) Node of the Network for Computational Nanotechnology (NCN/nanoHUB)[23] supports modeling and simulation of manufacturing processes. Methods for nanomanufacturing design are in synergy with the Materials Genome Initiative (MGI). The Advanced Manufacturing (AM) Program[24] includes support for nanoscale fundamental research to enable innovation in advanced manufacturing at universities exclusively or in collaboration with industry, and encouraging cross-disciplinary research.[25] The Future Manufacturing solicitation[26] has a goal of supporting fundamental research and education of a future workforce to overcome scientific, technological, educational, economic, and social barriers to enable new manufacturing capabilities that do not exist today.

In the area of semiconductors, NSF plans ongoing collaboration with other agencies and industry in activities such as the Semiconductor Synthetic Biology Circuits and Communications for Information Storage (SemiSynBio-III) program.[27] The three-year Real Time Machine Learning (RTML) program[28] (a collaboration with DARPA) has a focus on chip design AI. NSF will increase coordinated research on its Quantum Leap and Future of Work at the Human-Technology Frontier "Big Ideas" priority areas. Active centers in future computing include the STC on Quantum Materials and Devices, the MRSEC on Quantum and Spin Phenomena in Nanomagnetic Structures, and the Center for Quantum Networks ERC. Additional plans for 2023 funding include a Dear Colleague Letter on Quantum Manufacturing[29] and a program solicitation on the Future of Semiconductors.[30] Further collaboration is planned with industry groups developing hardware (with a focus on a "beyond Moore" system architecture and corresponding devices), software (with a focus on artificial intelligence), and implementation in various applications. The research will be conducted in collaboration with other agencies (e.g., NIH, DARPA).

In the areas of sensors and water, NSF is supporting research on materials and technologies that enable novel sensing mechanisms for biological, chemical, and nanoscale materials, including sensors for nanotechnology-related environmental, health, and safety research. It is also supporting projects in nanotechnology at the nexus of food, energy, and water systems through core nanoscience-related programs. In addition, the Nanotechnology Enabled Water Treatment Systems (NEWT) ERC, funded between 2015 and 2024, aims at developing high-performance water treatment systems that will broaden access to clean drinking water from a variety of unconventional sources (briny well water,

23 https://nanohub.org/groups/ncn/
24 www.nsf.gov/funding/pgm_summ.jsp?pims_id=505572
25 https://www.nsf.gov/pubs/2018/nsf18091/nsf18091.jsp
26 https://www.nsf.gov/pubs/2022/nsf22568/nsf22568.htm
27 https://www.nsf.gov/pubs/2022/nsf22557/nsf22557.htm
28 https://www.nsf.gov/pubs/2019/nsf19566/nsf19566.htm
29 https://beta.nsf.gov/funding/opportunities/quantum-manufacturing
30 https://www.nsf.gov/pubs/2022/nsf22589/nsf22589.htm

seawater, wastewater), and that will enable industrial wastewater reuse at remote locations such as oil and gas fields.

In March 2022, NSF announced the establishment of its new Directorate for Technology, Innovation and Partnerships.[31] Plans for 2023 that may involve nanotechnology-related investments include a Regional Innovation Engines initiative[32] intended to catalyze and foster innovation ecosystems across the United States to advance critical technologies such as nanotechnology; a Broad Agency Announcement for 2023 funding opportunities was released in May 2022.[33]

DOD supports R&D related to nanotechnology-enabled applications, devices, and systems in the department's laboratories and extramural programs. For example, NRL is developing photonically coupled quantum dot lasers for ultralow-power, ultrahigh-speed neuromorphic computing. It is also developing new approaches to interface with and control biological systems, including "protonic" devices for actuating cells and self-assembled nanoscale transducers that can photostimulate electrical activity in living neurons. In addition, NRL is developing dimensionally confined biological catalysts and multiscale architectures for chemical catalysts.

Planned 2023 investments for the ONR Power Electronics program include research on nanoclay insulation materials to further develop and characterize materials and their manufacturing processes, superparamagnetic nanocomposites for use in high-frequency transformers, and new ferrite-based soft nanocomposite magnetics and novel additive manufacturing methods for use in high-frequency transformers.

Ongoing and planned applied research at Army/ERDC includes developing a computational framework for the rational design of high-entropy alloy nanomaterials and to control nanomaterial microstructure (i.e., atomic arrangement) via thermal annealing. ERDC is advancing the use of nanomaterials, and materials modeling and characterization, to support requirements for advanced force-protection systems, e.g., graphene, carbon nanofibers, and other additives for modification of resins in composites, nanoceramic additives for hardening of metals, and nanomaterials with controlled optoelectronic properties for a variety of future sensing and coating applications. In collaboration with university researchers, ERDC is exploring the use of nanomaterial additions and nanoscale modifications to construction materials including graphene and nanoclay in asphalt, concrete, and composites to improve mechanical properties and durability. ERDC is also working with academia and industry to investigate new methods for integrating 2D printed nanotechnology-enabled sensors into 3D printed parts (including drones) for low-cost detection of environmental conditions (temperature, humidity) and gas detection in remote locations, and to investigate the use of graphene for applications in water treatment, multifunctional materials and sensors, and durable coating systems.

At DARPA, the Functional Materials and Devices program is exploring nanoscale materials that will enable new lightweight optical components and dispersed, tunable optical components that act as a controlled group, leading to applications in lightweight night vision systems with a wide field of view and the development of both active and passive obscurants that enable asymmetric visibility on the battlefield. The Atomic-Photonic Integration (A-Phl) program is focusing on technologies for high-performance atomic clocks and gyroscopes using integrated photonics and nanoscale atomic traps. The Precise Robust Inertial Guidance for Munitions (PRIGM) program is developing technologies for high-fidelity position, navigation, and timing (PNT) capability. The Magnetic Miniaturized and

31 https://beta.nsf.gov/tip/latest
32 https://beta.nsf.gov/funding/initiatives/regional-innovation-engines
33 https://sam.gov/opp/67236a938b4f49c5a582e6c57921e3bc/view

Monolithically Integrated Components (M3IC) and Ultra-wide Bandgap Semiconductors programs will focus on technologies for radio-frequency (RF) devices, including integrated magnetics and ultra-wide bandgap materials for higher-frequency and higher-power operation.

In September 2021, the Air Force Research Laboratory (AFRL) awarded a new seven-year cooperative agreement to the AIM Photonics Manufacturing USA institute, headquartered at the Albany Nanotech Complex in New York. Leveraged by additional contributions from participating companies, colleges and universities, and State governments, the funding will enable AIM to continue its work to develop advanced integrated photonics capabilities for a wide array of critical applications at the intersection of photonics and nanoelectronics, including telecommunications, chemical and biological sensing, artificial intelligence, and quantum information science.[34]

The DOE Office of Energy Efficiency and Renewable Energy (EERE) supports nanotechnology-enabled applications, devices, and systems through its Building Technologies, Solar Energy Technologies, and Advanced Manufacturing (AMO) offices. Within AMO, nanotechnology is supported in its Industrial Sector Decarbonization and Clean Energy Manufacturing (especially efforts within battery energy storage) sectors. Most of EERE's nanoscience-related efforts are supported out of AMO's Materials Supply Chain sector, with physical, chemical and biological science-based applied research (in particular the Atomically Precise Manufacturing effort) supporting AMO's goals in decarbonization through energy efficiency and electrification as well as through industrial greenhouse gas emissions reductions. The Materials sector also supports nanotechnology through its investments in energy-efficient ultra-precise microelectronic devices and systems and in nanocarbons and nano-processing for enhanced conductivity and harsh service condition materials R&D, demonstration, and deployment.

The DOE Office of Nuclear Energy (NE) invests in efforts to explain and control the nanoscale properties of materials used in nuclear applications, such as understanding radiation-induced changes to the nanometer-sized pores in fine-grained nuclear graphite, and modeling nanocluster evolution in irradiated ferritic oxide dispersion-strengthened (ODS) and ferritic/martensitic alloys. Additional efforts include application of nanotechnology-enabled testing techniques, such as nano-indentation, which is particularly important to nano-grained nuclear fuels.

The DOE Office of Fossil Energy and Carbon Management (FECM) plans investments in the development of high-value, coal-derived, solid carbon products/materials such as carbon fibers and nanomaterials (e.g., graphene, quantum dots, conductive inks, 3D printing materials, energy storage/battery anodes, carbon composites, and supercapacitor materials). FECM is also investing in nanotechnology-enabled sensors and controls, conducting gap analyses to develop automated awareness technologies, data integration tools, and blockchain technologies to harden potential targets.

A part of NASA's ability to enable humans to create a sustained presence in space will require power systems that are lightweight, reliable, operable under varying temperature extremes, and durable under exposure to the abrasive and attractive forces of Lunar dust. One NASA Space Technology Mission Directorate Early Stage Innovations (ESI) project is supporting university researchers to develop advanced nanomaterials that enable high-voltage power transmission on the Moon. The goals are to implement atomistic simulations and machine learning approaches to design, manufacture, test multi-layered copper-graphene wires for high-voltage power transmission, and develop a lightweight, multifunctional nanocomposite electrical insulator that can also serve as an electromagnetic interference (EMI) shielding layer.

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34 https://www.cto.mil/news/extension-to-aim-photonics/

NASA's nanotechnology investments also include research at two Space Technology Research Institutes (STRIs). The Center for the Utilization of Biological Engineering in Space (CUBES) supports deep-space biomanufacturing and integrates resource-use recovery in harsh planetary environments. One focus of CUBES that incorporates nanotechnology is in the area of biopharmaceuticals production, where university researchers are developing viral-immunosorbent nanoparticles to integrate into a biopharmaceutical synthesis/production process for astronauts to use on deep-space missions. Work continues under the Institute for Ultra-Strong Composites by Computational Design (US-COMP), which aims to develop carbon nanotube (CNT)-based composites with structural properties that exceed state-of-the-art carbon fiber composites. Materials development is being accelerated by using computationally guided design, as envisioned by the MGI. Structural CNT development being conducted by US-COMP complements technology maturation being carried out under the Superlightweight Aerospace Composites project funded by NASA's Game Changing Development Program.

NASA is working to develop lightweight CNT/Cu composite wiring with enhanced electrical conductivity through the Aeronautics Research Mission Directorate (ARMD) Transformational Tools and Technologies project. A new university collaboration has been established to improve NASA's previously developed copper plating technique, which should further enhance the intrinsic electrical conductivity and mechanical strength of CNT/Cu composite wiring. NASA is also collaborating with industry and academia to design and test various system-level nanotechnology-enabled components of future megawatt-class, high-power-density electric machines for electrified aircraft.

NIFA supports applied research on nanotechnology-enabled applications, devices, and systems for a wide range of agriculture, food, and environmental priorities. The scope includes rapid detection and effective intervention technologies for precision agricultural production; effective and efficient delivery of agricultural production inputs; ensuring food safety and biosecurity; developing effective treatments to improve animal health and novel value-added bionanomaterial products; and utilization and protection of natural resources, the environment, and agricultural production ecosystems.

NIFA's Agriculture and Food Research Initiative (AFRI)[35] invests in large integrated projects to promote the sustainable supply of abundant, affordable, safe, nutritious, and accessible food and other agricultural products, while enhancing employment and economic opportunities and improving the long-term health and well-being of Americans. This enables NIFA's goal to advance the convergence of agricultural science and technology with engineering, social sciences, and other disciplines, including biotechnology, omics, data science, artificial intelligence, nanotechnology, information sciences, cognitive science, and public engagement, to generate new scientific discoveries, new products, new markets and, consequently, new high-skill jobs. In doing so, it addresses interrelated challenges of agricultural productivity, water availability, food safety, environmental resilience, and nutritional security to ensure the economic, environmental, and social well-being goals of sustainable agriculture.

NIFA/AFRI's Foundational and Applied Science (FAS) program[36] supports nanotechnology for a wide range of issues facing agricultural and food systems, including the development of nanotechnology-enabled sensors for food and agricultural applications such as food safety and intelligent precision agriculture. Affordable sensor technologies and manufacturing that can be translated to commercial markets are particularly relevant to the food and agriculture sectors. NIFA is also exploring nanotechnology applications for improving the quality and quantity of agriculture water resources. The

[35] https://www.nifa.usda.gov/grants/programs/agriculture-food-research-initiative-afri

[36] https://www.nifa.usda.gov/grants/funding-opportunities/agriculture-food-research-initiative-foundational-applied-science

advanced food manufacturing program includes nanotechnologies to improve productivity, product quality, and safety—extending food shelf life and minimizing food waste and environmental footprints. FAS's Food and Human Health program supports investigation of food nutrients' impact on the gut microbiota for improving health, including enhancing the nutritional value of foods through improved absorption, nanoscale delivery, and the multidirectional impact of food composition and structure (including micro- and nanostructures) on human gut health.

The NIST 2023 request includes additional funds to initiate a coordinated effort in quantum materials design and characterization through development of a quantum materials program, and new instrumentation needed for neutron-based measurement technologies to rapidly advance the development of new quantum materials. NIST will continue to advance research on nanoscale devices and systems for a variety of applications, from microelectronics to coatings and pharmaceutical products. For example, NIST is developing laser-based methods for rapid measurement of the thermodynamics of single molecules, yielding insights on the molecular mechanism of nanopore detection of biomolecules and other polymer systems. The method provides a rapid assay for benchmarking nanopore biosensors and a measurement platform for single-protein sequencing. NIST is also working with FDA to develop nanoparticle tracking methods and microfluidic measurement devices to characterize complex liposomal products. The combination of deployable standards, measurement devices, and tracking methods will support accurate and economical measurements for quality control and of product equivalence.

NIST is developing standards and calibrations for super-resolution optical microscopy, improving the accuracy of localization measurements by orders of magnitude. This advances the reliability of localization data, correlation of nanostructure and optical signal, and throughput of localization metrology, with applications ranging from biological imaging to economical nanomanufacturing. Super-resolution optical microscopy and nanoparticle tracking methods are being developed to characterize microelectromechanical systems (MEMS), enabling novel measurements of motion in six degrees of freedom using ordinary optical microscopes. Such measurements are fundamental to understanding the behavior of MEMS devices, ranging from limits of intentional motion to emergence of unintentional motion. NIST is also developing nanofluidic measurement devices and super-resolution optical microscopy methods to characterize nanoplastics, potential environmental contaminants. These devices and methods enable characterization of nanoplastic structures and properties to improving understanding of byproduct heterogeneity and hazard.

Single- and multi-organ microphysiological systems that mimic the human body being developed at NIST can be used to evaluate efficacy and toxicity of new drugs, improve prediction of clinical outcomes, and reduce the number of animal experiments needed for new treatments to enter clinical trials. Complementary metal-oxide semiconductor (CMOS) bio-electronic devices are under development that enable highly multiplexed measurements of biomarkers at spatial scales ranging from molecular ensembles to biological cells and tissues. This modular platform technology is paired with self-assembled DNA nanostructures to allow sensing that can be adapted to biomarkers that rapidly evolve, such as viruses. The approach has the potential to transform numerous areas of biotechnology and human health, including surveillance for new pathogen threats and more timely clinical diagnostics. NIST is also developing systems and methods for a radiation dosimeter using both fluorescent nanodiamond and DNA co-located in an artificial organelle. This will enable research into genetic factors that differentiate the response to radiation by various organs and determine how malignancies become resistant to radiotherapy, which in turn will spawn disruptive technologies for diagnostic and therapeutic uses of radiation.

Forest Service nanotechnology research supports agency priorities of developing new applications for forest biomass removed from public lands to reduce wildfires. The primary focus is on understanding material properties and production of cellulose nanomaterials from wood, developing the science and technology for applications of cellulose nanomaterials in a broad range of products, and working with multisector partners to support commercialization of cellulose nanomaterials.

ARS nanotechnology efforts utilize sustainable agricultural-based feedstocks to developed value-added co-products. Ongoing and planned research themes include improving food safety to enhance and protect public health and agriculture through the development of nano-, micro- and macrotechnologies that safeguard food from pathogens, toxins, and chemical contaminants during production, processing, and preparation; developing healthful, value-added foods and enhanced bio-based products including biofuels; and reducing loss and waste through commercial nano-, micro-and macrotechnologies for postharvest processing, packaging, and storage.

Nanotechnology research at DOJ's National Institute of Justice supports its mission to provide objective and independent tools to reduce crime and advance justice. The application of nanotechnology to problems of crime and justice is an integral part of NIJ's R&D portfolio, particularly in the investigative and forensic sciences, law enforcement technology, and graduate research fellowships. NIJ funds nanotechnology research across its many programs, rather than through a single dedicated program, so total investments vary across fiscal years.

DHS is applying advancements in nanotechnology-enabled devices, materials, and systems to meet emerging needs, as well as improve on existing capabilities across the DHS mission space. This includes improving resilience to natural disasters and targeted attacks, leveraging advancements in nanotechnologies for advanced materials, sensors, nanomanufacturing, and biological systems. One ongoing project is a collaboration with the Army Core of Engineers and a university to explore the use of fiber-reinforced polymers in concrete infrastructure, with the initial focus on water infrastructure. For 2023 and beyond, DHS has an interest in research on novel materials for mitigating the impacts of extreme weather events on critical infrastructure such as dams and levees, as well as other nanotechnology applications that can be incorporated in building communities back better after a disaster. Potential applications include self-healing and regenerating materials and improved personal protective equipment. DHS also has interests in the use of nanosensors to detect threats and monitor the environment; advanced materials that are strong, flexible, and absorb heat and energy for rugged environments; and manufacturing advances to drive down the costs of these applications.

FHWA is pursuing nanotechnology-enabled solutions to improve the safety and performance of the Nation's transportation system. Development and deployment of high-performance nanomaterials shows great promise for improving the durability, resilience, and long-term performance of extant and future transportation infrastructure. Prior innovations in nanoscale characterization techniques and modeling material interactions at multiple scales are being leveraged to enable increased use of recycled or waste materials in infrastructure applications.

The Bureau of Reclamation's Science and Technology and Desalination and Water Purification Research programs support a range of activities from research- to pilot-scales related to water supply and power generation. Within that scope, USBR funds advanced water treatment projects aimed at enhancing water security by making previously unusable water sources viable for an identified beneficial use. This includes nanoscale research on a variety of topics, e.g., nanoplastic removal, nanotube coatings, and contaminant treatment/destruction processes.

PCA 3. Research Infrastructure and Instrumentation

The research infrastructure, including physical facilities and cyber resources, is critical to support the entire NNI ecosystem, and agencies will continue to invest in these important areas. The NNI R&D infrastructure also enables other priority research areas such as quantum information science, microelectronics, and the MGI. Agencies use a wide variety of mechanisms to support the research infrastructure, including center grants and instrumentation development or acquisition programs.

The DOE Office of Basic Energy Sciences operates five Nanoscale Science Research Centers (NSRCs),[37] national user facilities for interdisciplinary R&D at the nanoscale, including synthesis, fabrication, characterization, and theory/modeling. The NSRCs contain cleanrooms, nanofabrication resources, one-of-a-kind instruments, state-of-the-art microscopy, and other capabilities not generally available except at major user facilities. Operating funds enable scientific staff that performs cutting-edge research and provides technical support through the user programs at these facilities, which are made available to academic, government, and industry researchers with access determined through external peer review of user proposals. The NSRCs provide training for graduate students and postdoctoral researchers in interdisciplinary nanoscale science, engineering, and technology research. Recent and planned infrastructure investments at all NSRCs will expand and enhance capabilities at the intersection of nanotechnology and quantum information sciences, keeping these facilities at the leading edge of science and technology.

NIH/NCI continues to support the Nanotechnology Characterization Laboratory (NCL),[38] which conducts the characterization of nanomaterial formulations for imaging and therapeutic applications developed by researchers from academia, industry, and government. NCL receives a broad range of nanomedicine technologies through its Assay Cascade program, and has experience with virtually all nanoparticle platforms, therapeutic agents, and applications employed in the pursuit of better treatments and diagnostics for cancer. NCL has expanded efforts towards the evaluation of nanomedicine bioequivalence and assessment of personalized vaccine strategies and immunotherapies. NCL also has started evaluation of nanotechnology strategies for the diagnosis and treatment of COVID-19.

NIST provides scientists from academia, industry, and other government agencies with access to unique, world-class facilities and research instrumentation that help move the state of the art forward in emerging technology areas and advance understanding of nanoscale phenomena and systems. NIST continues to increase the research capacity to explore new electronic materials, devices, and process-structure-function relationships that accelerate lab-to-fab implementation. NIST facilities include the NIST Center for Neutron Research (NCNR) and the Center for Nanoscale Science and Technology (CNST) user facilities on the NIST Gaithersburg campus, the NIST Boulder Microfabrication Facility, and NIST capabilities at the National Synchrotron Light Source II (NSLS-II).

NCNR provides neutron measurement capabilities to the U.S. research community. It is a national center for research using thermal and cold neutrons, outfitted with a variety of instruments for neutron imaging, small-angle neutron scattering, reflectometers, diffractometers, and spectrometers.[39] The CNST NanoFab provides researchers with rapid access to state-of-the-art, commercial nanoscale measurement and fabrication tools and methods. The NanoFab's comprehensive toolset and

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37 https://nsrcportal.sandia.gov/
38 https://www.cancer.gov/nano/research/ncl
39 https://www.nist.gov/ncnr

dedicated technical staff enable users to process and characterize a wide range of nanoscale materials, structures, and devices.[40] The Boulder Microfabrication Facility enables development of nanoelectronic devices for chip-based quantum standards, sensors, integrated and quantum photonics, and advanced computing. Planned acquisitions include state-of-the-art tools for atomic layer deposition of coating on ultrathin films, plasma-enhanced chemical-vapor deposition, aluminum electron-beam deposition of Josephson junctions, and atomic force microscopy.[41] NSLS-II, located at Brookhaven National Laboratory, includes NIST beamlines based on “hard” x-rays, with two additional beamlines with “softer” x-rays. Nine end stations will take advantage of the unique broad and brilliant spectrum at NSLS-II to provide a world-leading suite of measurements of the atomic, molecular, and electronic structure of materials. A unique aspect of the NIST beamlines is the ability to measure samples with multiple beams, enabling the measurement of more diverse and complex structures such as in polymer-metal composites.

NIST is developing innovative focused-ion-beam machining processes to fabricate measurement devices and reference standards with high throughput and accuracy, including the use of sacrificial masks to transform the resolution–throughput tradespace, enabling ultrarapid prototyping and manufacturing of device arrays across wide fields, and super-resolution microscopy to quantitate beam placement and allow field correction.

Other ongoing NIST developments include novel tools and models to study the ultrafast dynamics of biomolecules, and methods to interpret and extract key dynamic and thermodynamic quantities from measurement. This work will improve the accuracy of biomolecule depictions in simulation for applications ranging from self-assembly to engineering molecular assembles into functional devices. NIST is also developing high-performance optomechanical devices to localize and control the interactions of photons, phonons, and electrons in nanoscale structures to enable new measurements for biological, chemical, and physical sensing; and ultrafast stroboscopic measurements of the subnanometer motion of mechanical resonators used in emerging high-impact technologies, including 5G wireless communications, precision timing, gyroscopes used in inertial navigation, and narrowband microwave filters.

The 2023 NSF request provides support for the National Nanotechnology Coordinated Infrastructure (NNCI),[42] including a national coordination office. Other STCs, ERCs, MRSECs, IUCRCs, and Centers for Chemical Innovation (CCI) have a focus on supporting the NNI, including the Center for Cellular Construction, two nanotechnology ERCs, one each on nanobiotechnology and cell technology, and a CCI that investigates the fundamental molecular mechanisms by which nanoparticles interact with biological systems. NSF will increase coordinated research on its Mid-scale Research Infrastructure priority area. The Major Research Instrumentation program[43] serves to increase access to multiuser scientific and engineering instrumentation, including instrumentation needed for NS&E activities, for research and research training in the Nation's institutions of higher education and not-for-profit scientific/engineering research organizations.

DOD supports research infrastructure and instrumentation via a number of mechanisms. NRL’s Institute for Nanoscience[44] conducts innovative, multidisciplinary research at the intersections of the

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40 https://www.nist.gov/cnst
41 https://www.nist.gov/programs-projects/boulder-microfabrication-facility
42 https://nnci.net/
43 https://www.nsf.gov/funding/pgm_summ.jsp?pims_id=5260
44 https://www.nrl.navy.mil/nanoscience/

fields of materials, electronics, and biology in the nanometer size domain. The laboratory serves as NRL's nucleus of collaborative activity in this rapidly evolving research area. The Army's Institute for Solder Nanotechnologies[45] is a team designed to leverage the unique capabilities of the U.S. Army, industry, and a leading research university. The ISN mission is to help the Army dramatically improve the survivability of the soldier by working at and extending the frontiers of nanotechnology through basic research, and by transitioning promising outcomes of that research in collaboration with Army and industry partners. The DOD-wide MURI program[46] involves teams of researchers investigating high-priority topics and opportunities that intersect more than one traditional technical discipline. Multi-year MURI awards are made in research topics specified by the participating defense agencies each year; as discussed elsewhere in this report, many of the topics involve nanotechnology. The Defense University Research Instrumentation Program (DURIP) supports purchases of major research equipment to augment current and develop new capabilities, enabling universities to perform state-of-the-art research that boosts the Nation's technological edge.[47]

Another example of a DOD PCA 3 investment is a partnership between AFRL and a university's synchrotron source to develop and validate innovative measurement tools to probe the structure of high-performance nanocomposites in real time during emerging low-cost manufacturing technologies via high-resolution x-ray microbeam scanning methods and phase-contrast imaging techniques. Applications under development in cooperation with other agencies range from flexible electronics to aerospace, agile manufacturing, and specialty nanomaterials.

NIFA invests in data science for food and agricultural systems to utilize data effectively, improve resource management, and integrate new technologies and approaches to further U.S. food and agriculture enterprises. Challenges associated with data in agriculture and food production and processing systems that are being addressed include data infrastructure and management; applications and use of data; entities affected by data; creation, collection, provenance, and characteristics of data; training programs for students, and knowledge needs around data; data principles and protocols; team, community, and public/private aspects of data; data producers, engineers, scientists, and researchers; roles of public, corporate, and commercial entities in data; privacy, security, confidentiality, and quality of data; biological and interoperable data systems; bibliometrics, altmetrics, and text and data mining; and data sharing, repositories, and analysis.

PCA 4. Education and Workforce Development

The NNI and continued nanotechnology innovation rely on STEM talent and a highly skilled workforce for every aspect of the R&D continuum. In addition to targeted nanotechnology education, the novel properties at the nanoscale can provide a spark to excite students to pursue STEM careers and help build a robust domestic workforce. NNCO and the NNI agencies use a variety of mechanisms to support public outreach and education from "K to grey" and emphasize opportunities and access to resources, especially for people in traditionally underserved communities. Many R&D programs support important aspects of education and workforce development. A few examples of targeted programs are identified here.

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45 https://isn.mit.edu/

46 https://www.onr.navy.mil/en/Education-Outreach/Sponsored-Research/University-Research-Initiatives/MURI

47 See the NNI Supplement to the President's 2022 Budget, p. 43, for an example of a nanotechnology DURIP investment: https://www.nano.gov/2022BudgetSupplement.

In 2023, NSF will fund education and workforce development activities in all areas of nanoscale science and engineering, including engaging the public. Typical activities supported by the Directorate for Education and Human Resources, the ENG Directorate's Division of Engineering Education and Centers, and other divisions are fellowships, traineeships/internships, single-investigator awards, and centers. Examples of projects at the undergraduate and graduate levels are Supporting Micro and Nano Technicians through Hybrid Teaching Methods[48] and Nano-Makerspace to Make and Explore in the World of the Small.[49] In addition, the Advanced Technology Education (ATE) program will offer support for nanotechnology education in 2023. A Dear Colleague Letter, Skills Training in Advanced Research & Technology (START),[50] provides students, faculty, and student/faculty teams in two-year higher-education institutions with experiential learning opportunities through research internships that involve IUCRCs and associated center research projects. A student internship program (INTERN)[51] for NSF-supported graduate students to gain training and experience in non-academic professional settings in emerging technologies, including nanotechnology, is being expanded. NSF and AFRL have entered into a partnership to support the training of graduate students through INTERN to meet NSF's strategic workforce development objectives as well as AFRL's mission to lead the discovery, development, and delivery of new technologies for air, space, and cyberspace forces.[52] In 2022, NSF and an industry semiconductor research consortium signed a five-year agreement to jointly support awards through the NSF Research Experiences for Undergraduates program for undergraduate students to gain hands-on experience in semiconductor-related research. This agreement will advance fundamental science and engineering in topics related to semiconductors and help develop a diverse workforce in this area of high national priority.[53]

NIFA supports curriculum development and future workforce training, including in nanotechnology. The AFRI Education and Workforce Development program[54] focuses on enhancing the three distinct components of the pipeline for developing the workforce in the food and agricultural sciences: (1) Enhancing Agricultural Literacy and Workforce Training offers institutional grants for in-service training, to provide K-14 educators increased knowledge of food and agricultural science disciplines and career opportunities and help them develop improved curricula to train the agricultural workforce for the future. (2) Developing Pathways offers undergraduates in food, agriculture, or allied disciplines the technical and leadership skills required for employment in the food and agricultural sectors or in graduate programs. (3) Advancing Science supports graduate and post-graduate education in agriculture and related disciplines. The program also supports predoctoral candidates and postdoctoral trainees.

Although the funding is reported in other PCAs, NASA regularly supports undergraduate and graduate-level scientists, engineers and faculty working on nanotechnology through its various aeronautics and space fellowship programs, including the University Leadership Initiative and NASA Space Technology Graduate Research Opportunity programs.

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48 https://nsf.gov/awardsearch/showAward?AWD_ID=2100402
49 https://www.nsf.gov/awardsearch/showAward?AWD_ID=1723511
50 https://www.nsf.gov/pubs/2021/nsf21076/nsf21076.jsp
51 https://www.nsf.gov/pubs/2021/nsf21013/nsf21013.jsp
52 https://www.nsf.gov/pubs/2021/nsf21029/nsf21029.jsp, https://www.afrl.af.mil/News/Article/2473878/new-afrl-collaboration-with-nsf-intern-program-opens-aperture-for-recruiting-to/
53 https://www.nsf.gov/news/news_summ.jsp?cntn_id=304304
54 https://www.nifa.usda.gov/grants/programs/afri-education-workforce-development

NIST, through its Office of Advanced Manufacturing, is supporting the Semiconductor Research Corporation to fund roadmapping needs across the full value chain for advanced packaging technologies and workforce development to support emerging microelectronics applications.

PCA 5. Responsible Development

The responsible development of nanotechnology has been an integral part of the NNI since its inception, and the initiative has proactively considered potential implications and technology applications at the same time. While agencies continue to build on the rich body of nanotechnology-related environmental, health and safety (nanoEHS) knowledge and to collaboratively protect researchers, workers, consumers, the general population, and the environment, the responsible development framework articulated in the 2021 NNI Strategic Plan has expanded. This PCA includes ethical, legal, and societal implications, issues of research integrity and security, and embraces an emphasis on inclusion, diversity, equity, and access (IDEA) and the responsible conduct of research.

In 2023, NSF will continue its funding for environmental, health, and safety (EHS) research primarily directed at understanding nano-bio phenomena and processes, as well as environmental, health, and safety implications and methods for reducing the risks of nanotechnology development. NSF continues to sponsor the Center for Sustainable Nanotechnology. ENG will fund this topic in its dedicated program, Nanoscale Interactions.[55] Other research in support of nanomaterials characterization, interfacial nanoscale phenomena, and exposure is performed in NSF's core programs. The NSF Directorate for Social, Behavioral and Economic Sciences addresses ethical, legal, and other societal implications (ELSI) related to nanotechnology. The ENG Directorate is funding award supplements on nanotechnology convergence for sustainable and responsible development, including U.S.-Africa collaboration.

FDA invests in nanotechnology research to help address questions related to the safety, effectiveness, quality, and/or regulatory status of products that contain engineered nanomaterials or otherwise involve the use of nanotechnology. FDA also invests in research to develop models for safety and efficacy assessment, as well as to study the behavior of nanomaterials in biological systems and their effects on both human and animal health. These investments support FDA's mission to protect and promote public health and helps to foster the responsible development of nanotechnology.

FDA's Office of the Commissioner, in partnership with the FDA Nanotechnology Task Force (NTF), facilitates communication and cooperation across the agency on nanotechnology research, both within FDA and with national and international stakeholders. NTF provides the overall coordination of FDA's nanotechnology research efforts in scientific staff development and professional training, laboratory and product-testing capacity, and collaborative and interdisciplinary nanotechnology research. FDA fosters and develops collaborative relationships with other Federal agencies through participation in the NSET Subcommittee, as well as with regulatory agencies, healthcare professionals, industry, consumers, and other stakeholders. NTF has increased its international efforts to strengthen global regulatory research activities aimed at developing novel characterization/measurement tools and consensus standards through the International Organization for Standardization (ISO), ASTM International, and the Organisation for Economic Co-operation and Development (OECD). FDA participates in the interagency interest group on nanoplastics, where scientists from more than 20 Federal agencies share interest, research, and resources available to advance the understanding of this emerging global issue. FDA scientists participate in other interagency and international coordination activities related to nanotechnology and nanoplastics, including the National Science and Technology

[55] https://beta.nsf.gov/funding/opportunities/nanoscale-interactions

Council (NSTC) Joint Subcommittee for Environment, Innovation, and Public Health, the Asia Pacific Economic Cooperation (APEC) Oceans and Fisheries Working Group, and the Global Summit on Regulatory Science.

The nanoEHS efforts of NIH's National Institute of Environmental Health Sciences (NIEHS) are designed to gain a fundamental understanding of the molecular and pathological pathways involved in mediating biological responses to engineered nanomaterials. Building on the previous efforts of the Nanotechnology Health Implications Research Consortium, current NIEHS-funded nanoEHS efforts include investigator-initiated research projects such as work focused on understanding how nanoparticle exposure modulates allergic lung disease using animal models. Planned activities in the NIH/NIEHS Division of Translational Toxicology include completion of analysis and reporting of studies evaluating immunotoxicity and chronic carcinogenicity of multiwalled nanotubes. The NIEHS Superfund Research Program plans to emphasize research that includes nanotechnology-enabled structures to enhance sustainable remediation and to enable rapid, accurate environmental monitoring. The NIEHS Small Business Innovation Research (SBIR)/Small Business Technology Transfer (STTR) program also supports research efforts for developing tools for nanomaterials exposure monitoring, including characterization of toxicity of airborne engineered nanomaterials (ENMs) using a direct *in vitro* exposure method and development of a third-party verification process for characterizing exposures to products containing ENMs.

NIOSH conducts toxicology studies that advance the understanding of potential human health implications of exposure to nanomaterials. NIOSH will evaluate biomarkers of exposure and disease using proteomic, metabolomic, and bioinformatic approaches; develop innovative *in vitro* methodologies to better predict *in vivo* outcomes; and evaluate pulmonary and dermal exposure and toxicity, and systemic toxicity that may result from occupational exposures, including effects in the cardiovascular, reproductive, neurological, and immune systems in response to wide variety of nanomaterials and nanotechnology-enabled products along the life cycle of the materials.

NIOSH will advance a more realistic view of the impact of nanomaterials along the life cycle by using real-world materials and exposure data to guide toxicology-testing regimens. These results will also be correlated with health studies conducted among workers at facilities where exposure evaluations are being conducted. The major objective of this approach is to gain a more realistic view of the impact of nanomaterials in their actual manufactured state.

To enable detection and measurement of airborne nanoparticles, NIOSH plans to develop, test, and evaluate direct-reading instruments. Additional plans include continuing field tests of the portable aerosol multielement spectrometer developed by NIOSH at nanomaterial producer and user facilities, as well as efforts in detection of airborne nanoparticles, including in biological systems, to evaluate and predict biological behavior and translocation between organ systems. NIOSH will also explore the feasibility of applying advanced sensing technology and data analytics to biomarkers as a means of evaluating nanomaterial exposure and possible early response.

NIOSH and CPSC are collaborating to study the release of ultrafine particulate and engineered nanomaterials from laser printer toner and from polymer-based 3D printers. An extensive study of metal-powder-based additive manufacturing is planned for 2023. NIOSH will collaborate with university partners and collaborators in private industry to promote safe practices in nanotechnology and advanced manufacturing. NIOSH plans to work with industry to develop practical, "real world" evaluation of hazard and risk represented by nanomaterials through their life cycles, focus the NIOSH field research effort on outputs that support sustainable nanomanufacturing, and collaborate with industry to assess the toxicology of carbon-based, metal-based, nanocellulose, and nanoclay-enabled materials.

In collaboration with a private industry trade organization, trade unions, and industrial partners, NIOSH plans to evaluate nanotechnology-enabled spray coatings, composites, and other nanomaterials in construction and manufacturing. It is also participating in the development of nanoEHS-related standards, e.g., ISO 23151—Nanotechnologies—Particle Size Distributions for Cellulose Nanocrystals, and OECD’s Test Guideline 110—Particle Size Distribution/Fibre Length and Diameter Distributions. The development of occupational safety and health guidance that can be incorporated into business plans to both protect worker safety and promote safe application development and commercialization will be a continued focus for NIOSH.

The NIST nanomaterial EHS research portfolio includes projects ranging from nanoplastics and reference materials to new measurements on consumer products and real-world environments. For example, NIST researchers are working with FDA and academia to investigate degradation of model polymers containing nanomaterials that exhibit barrier properties and that could have potential applications in the construction industry (e.g., outdoor coatings for corrosion-resistant infrastructure) and the food packaging industry (e.g., to extend ingredient freshness). This work addresses challenges in distinguishing nanomaterials from polymer matrices during polymer nanocomposite degradation, and evaluates how changes to the polymer nanocomposite morphology, including release of the nanomaterials, affects the potential exposure pathways of nanomaterials to their surroundings during use and disposal. NIST researchers are also investigating how different formulations of polyvinyl chloride (PVC) regulate the appearance, impact performance, and flammability of composite vinyl siding materials (which include micro- and nanoscale particles added to improve UV stability and impact performance) before and after UV exposure. NIST has completed UV exposure experiments on PVC with different composition/formulations at high temperature and high humidity. Chemical characterization and impact test analyses to simulate vehicle collision, hail, and debris during windstorms are ongoing.

EPA conducts research on emerging materials as part of the Chemical Safety for Sustainability National Research Program within the Office of Research and Development (ORD). This research is focused on developing, collating, mining, and applying information on engineered nanomaterials (including nanopesticides) and incidental nanomaterials (including micro-/nanoplastics) to inform both exposure and hazard assessments and support risk-based decisions related to the agency’s implementation of the Toxics Substances Control Act (TSCA) and the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). These efforts are coordinated with the Office of Chemical Safety and Pollution Prevention (OCSPP), which is responsible for implementation of these statutes. However, the information is important for other EPA program offices and external stakeholders.

Support for implementation of an improved evaluation framework for nanomaterials under TSCA and FIFRA is an ongoing need. Research activities include evaluating environmental release and assessing human and ecological exposures to engineered nanomaterials, including research to characterize the weathering, release, and transformation of nanomaterials from nanotechnology-enabled consumer products, such as emissions from 3D printers, as well as research to characterize the transport, transformation, fate, and environmental and health effects of nanotechnology-enabled pesticides and engineered nanomaterials. EPA supports ORD’s nanomaterials database (known as NaKnowBase), which captures the chemical and physical parameters of materials tested by EPA, the assays in which they were tested, and measured results. EPA is working in coordination with other Federal agencies to promote interoperability of NaKnowBase between NNI participating agencies. Furthermore, OCSPP is actively engaged in international co-operation efforts with OECD to develop new and/or improved test approaches and methods leading to better understanding of the human health and environmental hazards, exposure, and risks of nanomaterials.

NIFA supports nanoEHS research relevant to agricultural production and food applications. AFRI's Nanotechnology for Agricultural and Food Systems program supports projects on EHS assessments of engineered nanoparticles used in food and agricultural systems. This research includes detection and quantification of engineered nanoparticles; characterization of hazards and exposure levels; transport and fate of the engineered nanoparticles or nanomaterials in foods, crops, soils (and soil biota), water, and livestock (including aquaculture species); or exposures to agricultural and allied industry workers. The program also supports research on transport and fate of engineered nanoparticles or nanomaterials and nanostructures for nutrient delivery in food production, processing, and interactions with microbiota in the human gastrointestinal tract.

NIFA also supports research on economic and social implications of food and agricultural technologies, including nanotechnology. The broad social, ethical, cultural, legal, bioethical, and other potential impacts of emerging and disruptive technologies on society, agricultural markets, agricultural communities and rural prosperity, the food manufacturing industry, consumer preferences, and other domains are investigated. Multidisciplinary and interdisciplinary approaches involve physical scientists, legal scholars, bioethicists, social scientists, and researchers from the humanities, the public, and other stakeholders in assessing the technology's merits and risks. Research also includes examining modes of communication for effective public involvement in deliberations over these issues.

CPSC engages with Federal partners in a number of projects that are intended to characterize and quantify exposures to engineered nanomaterials released from products across the product life cycle. CPSC, EPA, NIOSH, and NIST collaborative work evaluates emissions, factors influencing emissions, and the potential toxicity from exposure to emissions from 3D printers, including the release and accumulation of nanoplastics. This interagency work is expanding to other types of 3D printers that are becoming more affordable to small businesses and the public, with an emphasis in 2023 on potential exposures to children. Information collected from these efforts will be used in the development of best practices for product use. This includes work with a university to develop a best practices white paper that will assist CPSC staff in applying current thinking regarding nanotoxicology when assessing the safety of products. The report will provide a risk management framework that includes evaluations unique to nanoscale properties of materials. CPSC and NIST are working on the optimization of *in vitro* test methods used to determine the toxic endpoints of nanomaterials. CPSC staff and partners are engaged in voluntary standards activities to create validated methods for quantifying and characterizing exposures from products, including an ISO project evaluating the release of nanomaterials from treated wood.

NCEH and ATSDR are conducting research on incidental micro- and nanoplastics, presenting at national and international professional events, identifying and addressing data needs to evaluate human exposures to micro- and nanoplastics, and reviewing the available scientific literature to quantify human exposures and risks. In 2021, they completed a scoping review to identify trends and gaps in the literature of micro- and nanoplastics in the environment that may threaten human health. Currently they are conducting a systematic review to understand potential human exposures to micro- and nanoplastics in water and health effects. Completion of a paper on this review is expected during calendar year 2023.

The Forest Service is developing research plans for technical and economic assessments of cellulose nanomaterials, life cycle assessments of cellulose nanomaterials, and EHS tools for chemically modified cellulose nanocrystals; however, the funding for the EHS projects is reported in other PCAs.

Consensus standards activities play an important role in developing confidence in the safety and efficacy of nanomaterials. For example, Federal agencies contribute to efforts in ISO TC 229's Working Group 3: Health, Safety and Environmental Aspects of Nanotechnologies, chaired by a U.S. industry representative.

Use of SBIR and STTR Programs to Advance Nanotechnology

As called for by the 21st Century Nanotechnology Research and Development Act, this report includes information on use of the Small Business Innovation Research and Small Business Technology Transfer programs to support nanotechnology development, as well as highlights of agency SBIR and STTR topics and other programs and activities that directly support the accelerated deployment and application of nanotechnology R&D in the private sector. Table 6 shows agency funding for SBIR and STTR awards for nanotechnology R&D from 2017 through 2020 (the latest year for which data are available). NNI participating agencies have supported over $2 billion in nanotechnology SBIR and STTR awards since 2004. Even though few agencies specifically call out nanotechnology in their SBIR/STTR solicitations, it is enabling innovations in many R&D application areas.

Table 6: 2017–2020 Agency SBIR and STTR Awards
(dollars in millions)

	2017			2018			2019			2020		
Agency	**SBIR**	**STTR**	**Total**	**SBIR**	**STTR**	**Total**	**SBIR**	**STTR**	**Total**	**SBIR**	**STTR**	**Total**
DHS	0.0	0.0	0.0	0.3	0.0	0.3	2.0	0.0	2.0	1.0	0.0	1.0
DOC/NIST	0.7	0.0	0.7	0.5	0.0	0.5	1.1	0.0	1.1	1.9	0.0	1.9
DOD	61.5	14.5	76.0	38.3	23.3	61.6	63.5	22.5	86.0	51.5	17.8	69.3
DOE	25.1	5.4	30.5	36.6	5.2	41.8	31.2	3.4	34.6	26.0	3.7	29.7
EPA	0.3	0.0	0.3	0.5	0.0	0.5	0.7	0.0	0.7	0.5	0.0	0.5
HHS/NIH	27.2	7.1	34.3	34.9	7.1	42.0	42.6	5.5	48.1	42.9	5.7	48.6
NASA	12.2	2.6	14.8	4.7	1.5	6.2	7.7	1.6	9.3	6.5	2.8	9.3
NSF	18.2	5.5	23.7	17.4	3.1	20.5	16.2	3.4	19.6	19.0	1.8	20.8
USDA	0.3	0.0	0.3	1.6	0.0	1.6	0.8	0.0	0.8	1.8	0.0	1.8
TOTAL	**145.5**	**35.2**	**180.7**	**134.8**	**40.2**	**175.0**	**165.7**	**36.4**	**202.1**	**151.0**	**31.9**	**182.8**

Some of the topics supported by agency SBIR and STTR awards (and enabled by nanotechnologies) include the following:

- High-resolution environmental sensing using drones enabled by nanoscale components (NSF).
- Real-time neural digitizers with 3D nanopatterned sensing electrodes for restoring connectivity in spinal cord injuries (NSF).
- Point-of-use nano-mosaic filtration technology for selective extraction of lithium (e.g., for battery components) from brine resources (NSF).
- Scalable production of functionalized electrospun nanofiber felts of regenerated cellulose for bioseparations (NSF).
- Carbon nanotube and polymer nanowire sensors for detecting chemicals and disease biomarkers (DOE and DOD).
- Discovery and development of vaccine adjuvants for improving the efficacy and durability of vaccines (NIH).

- Direct *in vitro* exposure method for characterization of toxicity of airborne engineered nanomaterials (NIH).
- Silicon nanomembranes for capturing and analyzing microplastics in environmental, consumer product, and drinking water samples (NIH).
- Nanoparticle-based filter technology for SARS-CoV-2 air filtration (NIH).
- Nanotechnology-enabled extraction of per-and polyfluoroalkyl substances (PFAS) *in-situ* from soil and groundwater (NIH).
- Adaptable RNA-based antibody platform for protection against contemporary/emerging human enteroviruses (NIH).
- Nanoparticle-based scintillator layer technology for dental x-ray imaging detectors (NIH).
- Multimodal platform using nanomaterials for oral screening for COVID-19 (NIH).
- Nanoscale, washable, flame-retardant treatments to fabrics for crew clothing (NASA).
- Multianalyte microfluidic colorimetric sensors for inorganic ions (NASA).
- Monitoring systems for inorganic and organic analytes in spacecraft water streams (NASA).
- Methods for the production and scale-up of novel MXene materials (DOD).
- Manufacturing of high-permeability materials by nanospray combustion for RF antennas (DOD).
- Nanoscale copper for power electronics thermal interfaces and low-temperature copper nanoinks for flexible electronics manufacturing (DOD).
- Improved performance and reduced cost in carbon nanotube fiber production (DOD).
- Nanomaterial discovery and synthesis platform for the fabrication of synthetic tissue/organ/nerve/skin sensors in medical training simulators and manikins (DOD).
- Multimaterials additive manufacturing to pattern custom-engineered magneto-dielectric nanocomposites, nanometals, and structural feedstocks for reduced-size conformal antennas with minimized radiation cross section (DOD).
- High-temperature, thermally conducting and insulating ferromagnetic binders and nanoencapsulation technologies for applying nanoscale coatings to fine powders to create mesostructured materials (DOD).
- Conformal electrolytes for high-energy-density rechargeable batteries with 3D arrays of nanoscale cathodes and anodes (DOE).
- Novel metal matrix nanocomposite coatings for spent nuclear fuel storage canisters to control stress corrosion cracking and radiation damage (DOE).
- Nanomaterial fillers for thermally conductive geopolymer grouts to reduce the cost of drilling geothermal wells for ground source heat pumps (DOE).
- Conductive lightweight hybrid polymer composites made from low-value recycled chopped/milled carbon fibers and graphene nanofillers through modification of carbon fibers, graphene sheets, and polymer matrices (DOE).
- Advanced manufacturing for novel energy-efficient dewatering methods for cellulosic nanomaterials (DOE).
- Novel probes for scanning tunneling microscopy (STM) tip-based atomically precise manufacturing (DOE).
- High-speed platform for highly parallel STM lithography and hierarchical assembly for nanoelectronics (DOE).
- Development of intelligent systems for atomically precise membranes, macromolecular catalysts, and therapeutics (DOE).
- Fabrication of high-quality zeolite membranes with a novel plate & frame configuration for molecular-scale mixture separations (DOE).

- Atomically precise structures and devices for catalysis: hierarchical zeolite catalysts for renewable surfactants platform (DOE).
- Atomic precision manufacturing for energy efficient microelectronics (DOE).
- Development of nanoparticles from microbial polysaccharides that can be used in food and pharmaceutical applications (USDA).
- Nanocomposite dielectric materials for energy-efficient manufacturing of printed circuitry (NIST).
- Reference materials for nanoscale particle size and concentration measurements (NIST).
- 3D nanofabrication platforms for manufacturing optical and photonic devices (NIST).
- Noncontact optical measurement methods for recycled polyethylene terephthalate glycol (PTEG) plastic panels to reduce power consumption during fabrication (NIST).
- Nanoelectromechanical systems (NEMS) probes for atomic imaging and sheet resistance characterization of thin films and semiconductor devices (NIST).
- Automated aqueous two-phase extraction for sorting of chiral-pure single-walled carbon nanotubes (NIST).
- High-precision 3D transmission electron microscope imaging systems (NIST).
- High-throughput, high-pressure small-angle neutron scattering sampling systems (NIST).

3. Progress towards the NNI Goals

The following selected highlights illustrate progress toward each of the five goals of the NNI. For more information and additional highlights, please see Nano.gov.

Goal 1. Ensure that the United States remains a world leader in nanotechnology research and development.

Central to the NNI is support for nanotechnology R&D, from the fundamental discoveries that expand the boundaries of knowledge to the applied and translational breakthroughs that enable new products and help address societal challenges. The individual NNI agencies utilize a variety of mechanisms to conduct and fund research that supports their respective missions. Collectively, these efforts support a vibrant and dynamic nanotechnology R&D ecosystem that is making critical advances in areas as diverse as advanced batteries and catalysts, medicine, multifunctional materials, next-generation computation, and space travel. These continued investments will enable future discoveries that build on the strong foundation developed over the course of the NNI and will ensure that the benefits to society and the economy are realized.

Harnessing nanotechnology to enable personalized medicine. Fighting cancer and other diseases using cells (e.g., T-cells) harvested from an individual is on the horizon if scientists can develop an approach to select the appropriate cells as determined from their time-dependent functions, such as cell killing, secretion, or movement. University researchers at an NSF ERC are answering this call by creating a digitally switchable micromagnetic structure using exotic multiferroic composites to capture, study, and release individual cells defined by their functionality to enhance personalized medicine and fight diseases.[56]

Understanding cancer at the nanoscale to inform better therapies. University researchers at an NSF NNCI node, and funded by NIH, DOD, and a private foundation, have shown that nanotubes generated by cancer cells can steal immune cells' energy sources by excising the immune cell mitochondria. New insights like this into how cancer evades the immune system could enable the realization of the full potential of immunotherapies to overcome cancers.[57]

Driving the next generation of therapeutics with vaccine adjuvants and nanotechnology. Vaccine adjuvants can improve the efficacy of vaccines for use in preventing or treating infectious disease, allergic disease, autoimmune disease, cancer, and substance use disorders. Vaccine adjuvants augment and help guide immune responses, including induction of durable protection. Certain populations, such as people with compromised immune systems, pregnant women, older adults, and the very young, particularly benefit from adjuvanted vaccines because their immune systems have unique characteristics and needs for developing protective immunity. Through NIAID adjuvant programs, NIH-supported researchers have led the field of adjuvant science through discovery and development of novel vaccine adjuvants by engineering the chemical and physical properties of materials at the nanoscale. These vaccine adjuvants have then been leveraged to advance the development of effective COVID vaccines,[58] novel immunotherapy approaches for the treatment of allergy,[59] and the development of opioid vaccines through the NIH Helping to End Addiction Long-term (NIH HEAL) initiative.[60]

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56 https://doi.org/10.1002/adma.202006651

57 https://doi.org/10.1038/s41565-021-01000-4

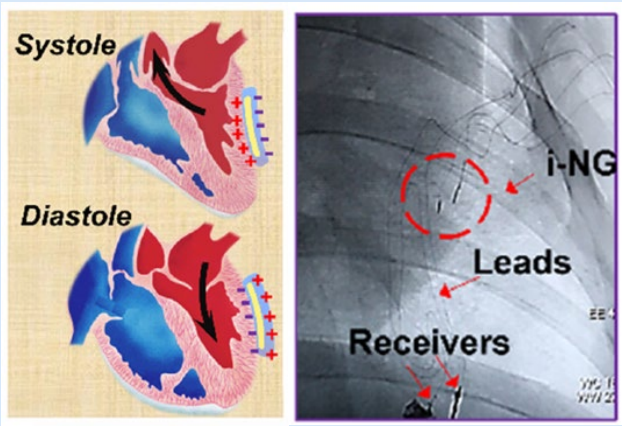
58 https://www.niaid.nih.gov/news-events/adjuvant-developed-nih-funding-enhances-efficacy-indias-covid-19-vaccine

59 https://pubmed.ncbi.nlm.nih.gov/31300280/

60 https://heal.nih.gov/news/stories/OUD-vaccine

Repairing spinal cord injuries. University and AFRL scientists, with support from NSF, NIH's National Institute of Neurological Disorders and Stroke, and private foundations—and using facilities at DOE's Argonne National Laboratory—have developed a new injectable therapy that reverses paralysis and repairs tissue after severe spinal cord injuries. The researchers administered a single injection to tissues surrounding the spinal cords of paralyzed mice. Just four weeks later, the animals regained the ability to walk. A key part of this therapy is that bioactive signals are sent to trigger cells to repair and regenerate. Injected as a liquid, the therapy immediately gels into a complex network of nanofibers that mimic the extracellular matrix of the spinal cord. [61]

Developing nanotechnology-enabled power sources for pacemakers



Images of the implantable nanogenerator (i-NG) device. When the heart beats, it flexes the nanogenerator device which generates energy (left). X-ray image shows an implanted device in an animal model (right). Image credits: University of Wisconsin–Madison.

NHLBI-funded researchers are developing a power source for intracardiac pacemakers composed of an implantable nanogenerator with a miniaturized supercapacitor that automatically powers a pacemaker by harvesting energy from heartbeats, a self-sustainable power source. They developed a flexible, micro-grating implantable nanogenerator capable of converting the organ motion to continuous alternating current desired for efficient capacitor charging. The nanogenerator is composed of a piezoelectric polymer film with a 5 nm layer of chromium and a 50 nm layer of gold deposited on both sides of the film. In different stages of cardiac activity, systole and diastole, the device bends inward and outward, respectively. The bending of the nanogenerator creates a potential difference due to its deformation. The device tracks heart function in real time, allowing for an effective response to heart attacks. After implantation, the device was found to leave cardiac structure and function unaltered, and have very mild reactions over the course of the study. This nanogenerator technology can be used to power other small electronic implants in addition to pacemakers.[62]

Advancing nanotechnology-enabled biomarker analysis. NCI-funded researchers developed tools for analysis of biomarkers on circulating extracellular vesicles (EVs) using a 96-well assay that integrates enrichment of EVs by antibody-coated magnetic beads and electrochemical detection. Unlike other methods that typically have lengthy sample workups, limited throughput, or insufficient sensitivity, this newly developed assay can be performed in less than one hour. The assay was used with a combination of antibodies for clinically relevant tumor biomarkers (EGFR, EpCAM, CD24, and GPA33) of colorectal cancer (CRC) in plasma samples from 102 patients with CRC and 40 non-CRC controls. Such rapid assays may aid cancer detection and patient monitoring.[63]

Defining surgical margins with nanotechnology. Researchers funded by NCI performed clinical testing of a tool for intra-operative management of the surgical margin in patients diagnosed with head and neck squamous cell carcinoma (HNSCC). They evaluated a standardized, specimen-driven, pH-

[61] https://doi.org/10.1126/science.abh3602
[62] Figures from https://doi.org/10.1016/j.nanoen.2021.106507
[63] https://pubmed.ncbi.nlm.nih.gov/34183802/

activatable, fluorescent imaging agent for the purpose of clinical decision-making during surgery. Tests on 13 HNSCC patients showed that the technique allows for sharp tumor delineation, giving surgeons a clinical tool for real-time margin assessment with high sensitivity.[64]

Building nanostructures to fight inflammation. NIBIB-supported researchers have developed nanofiber-based treatments using supramolecular self-assembly. These nanofibers are designed to serve as an alternative strategy to monoclonal antibody treatment for autoimmune disorders.[65]

Addressing cryopreservation with nanotechnology. An NHLBI-funded investigator-initiated research project is developing magnetic nanoparticles that can be heated using RF radiation to overcome major clinical and research gaps in cryopreservation for organ transplantation. They demonstrated that this novel nanomaterial, along with lower radio frequencies of less than 1 MHz and alternating magnetic fields, can generate heating rates rapid enough to avoid organ damage.[66]

Conducting fundamental research to inform regulatory review of nanotechnology-enabled products. FDA's National Center for Toxicological Research (NCTR) is conducting collaborative regulatory science research on the advanced characterization, safety, and biodistribution of nanomaterials in FDA-regulated products. Current active research at NCTR includes safety and efficacy of nanomaterials, including sex-based differences in immune response to nanoparticles; biochemical, genetic, and neurotoxicology; effects on microbiota; generic drug products containing nanomaterials; and standards development.

Advancing nanoscale catalysis. Advances in catalysis enabled by nanotechnology have the potential to benefit multiple industries that are critical to the health and the national, economic, and energy security of all Americans. NNI agencies have been supporting research in this field that shows considerable promise. For example, DOE-supported national laboratory and university researchers developed a new catalyst consisting of individual platinum (Pt) atoms that is highly efficient and reversible in dehydrogenation and rehydrogenation of large cyclic hydrocarbons. Porous CeO_2 nanorods were synthesized and employed as supports to isolate single Pt sites. The new catalyst displays over 300 times higher reaction rates than commercial Pt nanoparticle catalysts for large molecule reactants. This work will pave the way for further rational design of highly efficient catalysts for sustainable energy conversion and storage.[67]

NRL has demonstrated the use of vacuum field catalysis, which has unique potential in the area of pharmaceutical synthesis, where slight chemical changes result in completely different biological activity, and has implications for energy storage and transfer via control of protonation equilibria. Scientists at NRL also have developed a modular chemistry utilizing nanoparticles to enable enzymes to be brought into close proximity of each other and engage in highly-efficient channeled biocatalysis, harnessing the power of enzymes to make bulk precursor and specialty chemicals from a common starting material. This technology can allow for on-site synthesis of foods, fuel, and medicine. Another NRL team designed catalytic aerogel–based scaffolds from covalently networked nanoscale oxides capable of dissociating molecular oxygen (titania, ceria) and characterized their interaction with supported metal (Au, Cu) nanoparticles (NPs). The team found that electron communication with oxygen vacancies in the oxide network supported Cu NPs sufficiently metallic that the NPs sustain surface plasmon resonance and maintain high activity during oxidation of carbon monoxide (CO), an important process in synthetic fuel production. NRL is studying the stabilization of the catalytically

64 https://pubmed.ncbi.nlm.nih.gov/34031845/
65 https://doi.org/10.1073/pnas.2018627118
66 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8498880/
67 https://doi.org/10.1038/s41467-022-28607-y

active phase of Ni(II) supported on ceria for CO oxidation by intimately contacting the $Ni(OH)_2$ NPs throughout a ceria aerogel morphology under oxidizing conditions, yielding high activity for CO oxidation even in the presence of water. It is also examining how ceria aerogel–supported Cu NPs preferentially oxidize CO in an H_2 feedstream, maintaining on-stream durability even in the presence of water, with minimal oxidation of H_2 at the operating temperatures of proton-exchange membrane fuel cells.

University researchers supported by NIFA and NSF have developed highly efficient peroxidase mimic–nickel–platinum nanoparticles that consist of nickel-rich cores and platinum-rich shells and that have record high catalytic efficiency. The researchers used density functional theory calculations to show that the unique surface structure of their nickel–platinum nanoparticles weakens the adsorption of key intermediates during catalysis, boosting catalytic efficiency. The research team demonstrated the use of the nanoparticles in an enzyme-linked immunosorbent assay (ELISA) for cancer, achieving 300 times greater sensitivity than conventional enzyme-based assays in detecting carcinoembryonic antigen, a biomarker used to detect colorectal cancers. The technique could be used to detect biomarkers for other types of cancers and other diseases.[68]

Exploring, expanding, and exploiting the properties of nanomaterials. ISN researchers are studying the mechanical response of nanoengineered hydrogels to improve understanding of tissue damage and to design and fabricate better protection materials. They have discovered and characterized a new type of elastodynamic instability in hydrogels subject to strong converging shock loading and confirmed that this is a unique feature of soft materials with high tensile strength; experimentally and theoretically studied the impact of topological defects on fracture and fatigue of soft materials; fabricated fatigue-resistant nanofibrous hydrogels for potential armor applications; and conducted dynamic testing of a thin fatigue-resistant hydrogel, revealing impact resistance comparable to polyethylene. They also fabricated a new form of ultra-strong 2D polymer through irreversible 2D polymerization that was previously considered impossible. The resulting material (2DPA-1) shows exceptional 2D elastic modulus and ultimate strength in well-aligned nanofilm form as a consequence of high-density interlayer hydrogen bonding. This novel amide-based 2D polymer opens up avenues to new classes of lightweight, structural materials for shock mitigation. Complementary ISN projects have underscored the importance of intermolecular hydrogen bonding interactions on microstructure and on energy dissipation mechanisms including dynamic stiffening; enabled tuned materials synthesis for enhanced material strength, toughness, and energy dissipation; and explored force protection and shielding applications of superlastic zirconia shape memory ceramics, as well as 2D materials such as graphene and hexagonal boron nitride (hBN).

University researchers supported by ARO have also progressed in developing impact- and wear-resistant nanomaterials, as well as coating technologies for extreme operating environments: they investigated the ability to tune strength and toughness of multilayered composite films through a competition of nanoscale deformation mechanisms between layers. The work built upon a recent discovery of an atomic-scale rippling phenomenon in layered structures, termed “ripplocations.” Simulations showed how initial buckling behaviors self-align into ripplocation boundaries. The group validated these simulations by performing nanoindenations and observing the deformations using scanning tunneling electron microscopy, revealing kink band structures with distinct delamination cracks on either side. Experimental studies on Nb-Ti_2AlC and Ti-Ti_2AlC layered systems showed 200-

[68] https://doi.org/10.1021/jacs.0c12605

400% increases in strength while also retaining ductile behavior, avoiding the typical trade-off of strength versus toughness.[69]

Researchers at AFRL are investigating shock-induced deformation of polymer nanocomposite thin films, using polymer-grafted nanoparticle assemblies in homopolystyrene, which provide robust mechanical resilience. They observed a size and shape effect dictating the transition from viscous to glassy behavior, which was also highly rate-dependent. Shock loading promoted ductility (due to the extreme rate of heating and localization), leading to extreme deformation/drawing and energy absorption during impact of these polymer thin films, which could enable next-generation armor concepts and mechanical dissipators. These materials could serve as possible protection materials or as binder materials for energetics, taking advantage of the mechanical dissipation effects at extreme loading rates.[70]

AFRL is researching the use of catechols to functionalize exfoliated MXene ($Ti_3C_2T_x$) nanosheets in colloidal suspension. Researchers used density functional theory and ultraviolet–visible spectroscopy (UV–vis) to confirm that catechols react spontaneously with $Ti_3C_2T_x$ surfaces, where binding is initiated, and used x-ray diffraction to verify that catechol functionalization increases $Ti_3C_2T_x$ sheet interlayer spacing. They also demonstrated immobilization of fluorescent dye on the MXene surface.[71] Tailoring MXene surfaces via aqueous functionalization with catechols, where colloidal stability can be modified and further functionality can be introduced, could enable the development of MXene-based thin-film nanocomposites with tailored properties. Another AFRL research group has developed an efficient, room-temperature etching method using halogens in anhydrous media to synthesize MXenes from Ti_3AlC_2, offering opportunities to modulate MXene properties through controlled surface chemistries.[72] These and other recent advances open the door to a wide variety of potential applications of MXenes and other multifunctional architected nanocomposites, including EMI shielding, multifunctional coatings, electrostatic discharge protection, displays, and wearable electronic devices.[73]

Under the DARPA Fundamental Limits and Non-Equilibrium Materials programs, new nanoscale devices are being developed that push the physical limits of sensing, computing, and timekeeping. This research has led to structured media devices with extreme nonlinear interactions with light for sensor protection and thermal energy management. Other outcomes include foundational demonstrations of topological read/write memory devices, a record-breaking atomic clock, quantum coherence, and logic-gate fidelity. This work has also led to the discovery of a novel non-equilibrium phase of matter, i.e., discrete time-crystals (DTCs).

Exploring the frontiers of electronic and photonic materials. AFRL researchers are advancing the boundaries of materials science in understanding and manipulating the properties of a variety of electronic materials systems, including ferrielectric heterostructures, gallium-based liquid metal alloys, multiferroic van der Waals layered materials, ionically conductive van der Waals ferroelectrics, polar van der Waals chalcogenophosphates, and tunable quadruple-well ferroelectric van der Waals crystals. They have developed advanced instrumentation techniques to probe the properties of these materials, and explored applications such as coupling of flexibility and conductivity (gallium-based liquid metal alloys), sensors (layered multiferroics), low-energy nanoelectronic integrated circuits (ionically conductive van der Waals ferroelectrics), novel nanoelectronic device architectures (layered

[69] https://doi.org/10.1016/j.mattod.2020.11.014
[70] https://doi.org/10.1021/acsnano.0c06146
[71] https://doi.org/10.1021/acs.langmuir.0c03078
[72] https://doi.org/10.1021/acsnano.0c08630
[73] https://doi.org/10.1021/acsnano.0c09834

ferrielectric materials), and data storage (tunable ferroelectric van der Waals crystals). They also developed a maskless, resist-free, and fully reversible process to engineer defects in graphene using electron-beam chemistry with radiolyzed water. This process was performed inside a variable pressure scanning electron microscope by generating radiolysis products using reactions between the e-beam and water vapor, which in turn reacted with the graphene at the location of the probe. These reactions enabled controlled chemistry on the graphene surface at a resolution of ~60 nm and hence created defects in precise locations defined by the e-beam. The density of sp3-type defects that were detected was tuned by varying the e-beam dose. In addition, these defects were cycled in and out of graphene by alternating e-beam chemistry and thermal annealing. This reversibility promises future applications of e-beam chemistry in reconfigurable plasmonics and electronics.

Harvesting potable water from thin air. DOE-supported university researchers have created a material that can collect drinkable water from the air both day and night, combining two water-harvesting technologies into one. The material is part of a class of micro- and nano-architected materials whose shapes (controlled at each length scale, nanoscopic and microscopic) give them unusual and useful properties. In this case, the material is a hydrogel membrane of arrayed tiny spines and are inspired by the shape of cactus spines. A rooftop prototype system with a 55 cm^2 membrane produced ~185 mL of fresh water over eight days through a combination of solar evaporation under natural sunlight and via fog capture at night.[74,75]

Enabling interstellar space exploration. University researchers supported by NSF and a private foundation are designing a laser-powered light sail that could carry a microchip-sized probe at a fifth of the speed of light, fast enough to make the trip to Alpha Centauri in roughly 20 years. The group has demonstrated multiscale photonic structures and nanophotonic crystal slab reflectors composed of molybdenum disulfide and crystalline silicon nitride, offering insights into how nanoscale patterning within the sail could most efficiently dissipate the heat from a powerful laser.[76] They also analyzed the optimum shape to reduce mechanical stresses and avoid tears in light sails with nanometer-scale thicknesses that are rapidly accelerated to relativistic velocities by lasers.[77]

Developing smart textiles for myriad applications. Researchers at ISN have developed a fabric that transduces nanometer scale mechanical vibrations to an electrical output using synergistic coupling of a multimaterial piezoelectric fiber with a fabric medium composed of high-modulus textile fibers in the weft of a cotton warp. This construction converts tenuous 10-7 atm pressure waves at audible frequencies into lower-order mechanical vibration modes of 1-1000 nm. Within that medium, a single strand of thermally drawn piezoelectric elastomeric fiber is woven, leading to a fabric that transduces sound. Potential applications include a fabric that could measure the precise direction of an acoustic impulse with ~1-degree accuracy, bi-directional communications between two fabrics working as sound emitters and sound receivers, and wearable fiber-based detection of cardiac sound signals (i.e., a wearable stethoscope).

Harnessing bacteria to synthesize high-performance nanomaterials. University researchers funded by NIFA, ONR, and DOE have used genetically engineered bacteria to produce polymeric amyloid fibers that exhibit ultimate tensile strength comparable to the strongest natural spider silk (~1 GPa, stronger than common steel) while displaying higher toughness than natural spider silk (~160 MJ/m^3).

[74] https://doi.org/10.1038/s41467-021-23174-0

[75] See the NNI Supplement to the President's 2022 Budget, p. 31, for additional information on this subject, including complementary work supported under the DARPA Atmospheric Water Extraction program: https://www.nano.gov/2022BudgetSupplement.

[76] https://doi.org/10.1021/acs.nanolett.1c03273

[77] https://doi.org/10.1021/acs.nanolett.1c03272

Redesigning the silk sequence by introducing amyloid sequences that have a high tendency to form β-nanocrystals, they were able to induce the bacteria to synthesize a hybrid polymeric amyloid protein with 128 repeating units. The resulting proteins had less repetitive amino acid sequences than spider silk, making them easier for engineered bacteria to produce. The polymeric amyloid proteins can be wet-spun into macroscopic fibers with a wide range of mechanically demanding applications. This strategy for design and biosynthesis of long-protein fibers could be expanded to create numerous other functional materials.[78]

Generating hydrogen fuel from nanostructured metals. A team of ARL researchers has developed, patented, and licensed a nanogalvanic aluminum alloy powder technology that has demonstrated the ability to generate large volumes of hydrogen gas when mixed with any liquid that contains water. These nano-grained alloys are also structurally strong, and can be fabricated in powder form, making them attractive feedstocks for both conventional and additive manufacturing processes. The ability to print complex components, e.g., truss structures or plumbing for a circulatory system, is one example of how this technology could link materials, processes, and design of robots, drones, or UAVs. It could even enable a "self-cannibalizing" robot where the nanogalvanic alloy used in its structure could serve as a fuel of last resort.

Advancing the frontiers of nanophotonics. ISN researchers are reporting progress on a number of projects that are exploring the frontiers of nanophotonics science, with significant opportunities for both civilian and military applications. One project has provided new and detailed understanding of novel quantum dot up-conversion mechanisms with applications in terahertz (THz) and infrared (IR) sensing, demonstrated additional mechanisms for both sensing and THz/IR ultrahigh-bandwidth modulation and photonic control, and demonstrated the first all-optical control over quantum dot photoluminescence blinking. Another developed a general framework to control scintillation with nanophotonics. Scintillation is a physical phenomenon through which high-energy particles are converted into visible light when bombarding a scintillator material (typically, a semiconductor, an amorphous material doped with defect states, or a dense ceramic doped with rare-earth materials). The research group's combined experimental and theoretical framework enables first-principles design of nanophotonics-enhanced scintillators, as well as powerful spectroscopic techniques to infer the spectral and energetic properties of the scintillating materials. A third project is harnessing high-temperature nanophotonics to explore new physical phenomena that enable unprecedented control of thermal radiation and radiative heat transfer at the nanoscale and at very high temperatures (>800°C), demonstrating novel materials, devices, and system-level applications ranging from mesoscale thermophotovoltaics, to small-scale radioisotope power sources, to non-conventional IR light sources and room-temperature IR detectors.

AFRL scientists are investigating quantum nanophotonic interactions of monolayer transition metal dichalcogenide MoS_2 films. These and other 2D materials could enable next-generation optical coatings and devices, due to their potential for controlled optical behavior. They showed that variability in the optical response of these materials can correspond to changes in oscillator amplitude and dielectric polarizability of excitons—suggesting promising charge transfer and local dielectric media effects. They also observed reversible changes in refractive index by varying n- and p-type chemical adsorbates, and that dopant-induced screening of MoS_2 optical constants is dependent on film quality, suggesting that pre-existing structural defects have a dominant role in determining the optical properties of films.

78 https://doi.org/10.1021/acsnano.1c02944

Tailoring the optical constants of these materials in a reversible manner could have broad impacts on development of quantum optical and optoelectronic devices.[79]

Under the DARPA Functional Materials and Devices program, novel nanomaterials and optics with enhanced photon up-conversion bandwidth and efficiency are enabling new lightweight night-vision systems. The focus of these and other technologies is to convert sufficient light to enable night vision without the need for traditional headgear.

NIST researchers have demonstrated exponential decay free wave propagation in a purely lossy medium.[80] Usually, when light travels through a medium, absorption and scattering rapidly diminish the intensity of the light beam, and it loses a fixed percentage of energy per unit distance traveled. That decline—known as exponential decay—holds true for light traveling through any fluid or solid that readily absorbs and scatters electromagnetic energy. The researchers observed up to 400-wave deep polynomial wave propagation accompanied by a uniformly distributed energy loss across a nanostructured photonic slab waveguide, and used coupled-mode theory and vectorial electromagnetic simulations to predict deep wave penetration and spatially constant radiation losses through the waveguide region, regardless of length. The uncovered exponential decay free wave phenomenon is universal and holds true across all domains supporting physical waves. Practical applications include generating large, uniform, and surface-normal free-space plane waves directly from dispersion-engineered photonic chip surfaces. In another project, NIST researchers demonstrated that superconducting nanowires can efficiently detect single photons with wavelengths up to 10 micrometers, five times longer than previously possible.[81] These infrared wavelengths are emitted when bodies radiate heat. The ability to detect photons at these wavelengths opens opportunities for applications such as an enhanced search for chemical signs of life on other planets, stealth navigation of vehicles in pitch darkness, and the search for dark matter.

University researchers supported by NSF, AFOSR, and NASA have developed an attachment that can turn just about any camera or imaging system into a polarization camera. The attachment uses metasurfaces of sub-wavelength nanopillars to direct light based on its polarization and compiles an image that captures polarization. The device has been demonstrated on an off-the-shelf machine vision camera, by screwing it on in front of the objective lens. This technology could be used to improve machine vision in self-driving vehicles, for remote sensing, or in biometric security sensors, among many other applications.[82]

Using theory, modeling, simulation, and artificial intelligence to enhance nanomaterials design. NNI participating agencies are supporting a wide variety of research that is integrating the use of advanced modeling, computational and experimental tools, and quantitative data to optimize and accelerate development of nanomaterials, in synergy with the goals of the MGI. An ONR-supported university team developed a new computational method to design interactions between nanostructures that assemble into a target structure and avoid undesired competing assemblies. This enabled the first-ever reported system of two distinct particle types that assemble into cubic diamond lattice structure without defects.[83] The team also developed a new interactive tool to design and simulate DNA nanostructures assembled into a 3D lattice.

79 https://doi.org/10.1021/acsphotonics.1c00183
80 https://doi.org/10.1038/s41565-022-01114-3
81 https://doi.org/10.1063/5.0048049
82 https://doi.org/10.1364/OE.450941
83 https://doi.org/10.1103/PhysRevLett.125.118003

ERDC is investigating the superior shock wave and ballistic mitigation capacity of thin films (< 500 nm) and nanolayered materials through large-scale physics-based atomistic simulations and high-rate testing, including nanoindentation and microparticle ballistic testing, to inform the optimization, synthesis, and testing of a multilayered nanosystem for enhanced ballistic mitigation. ERDC researchers are also investigating a computational framework for the rational design of high-entropy alloy nanomaterials to control their microstructure via thermal annealing.

A new computational model for the development of segregation-stabilized nanocrystalline alloys is under development by ARO-supported researchers. These alloys utilize a solute as a means to keep the individual crystals (grains) of the material at the nanoscale. Most computational methods assume uniform distribution of the solute in the material; the new method takes into account the preference of various solutes to segregate at different types of grain boundaries. This research lays the foundation for designing nanocrystalline alloys that employ alloy segregation for potential hypersonic applications.

FHWA has been supporting research on multiscale (including nanoscale) modeling to better understand the behavior and properties of infrastructure materials, including the hydration of portland cement.[84]

University researchers supported by NIH/NIAID used atomistic molecular dynamics simulations to understand interactions between nanoparticles coated with sulfonated ligands, which can exhibit virucidal activity against multiple viruses, and segments of human papilloma virus type 16 (HPV16) capsids. They showed that that the nanoparticles bind primarily at the interfaces of two HPV16 capsid proteins, and that this binding can break the contacts between the neighboring proteins. This work suggests that targeting the interfaces between pairs of capsid proteins could provide a pathway for the design of new generations of broad-spectrum virucidal materials.[85]

Using DNA to assemble complex nanomaterials. DOE/BES-funded university researchers using resources at the Center for Functional Nanomaterials and the National Synchrotron Light Source II created DNA nano-chambers with bonds that can control the assembly of targeted nanoparticle structures. The method forms DNA strands into hollow cubes that can carry nanoparticle cargoes. The DNA strands that extend from the cube are encoded with specific assembly directions. This binding information allowed the scientists to precisely control the orientation of the objects in each direction at each step along the assembly pathway.[86] DOE/AMO-funded university and research institute researchers have developed two different ways to actuate DNA origamis in 2D for printing. One method uses DNA strands, the other uses thermal energy.[87]

University researchers supported by ONR are designing, fabricating, and characterizing DNA-scaffolded molecular dye aggregates, using dyes with custom-tailored structures, to improve the fundamental understanding of how dye structure-property relationships are central to realizing molecular excitonic energy transfer and excitonic quantum computing. The researchers applied time-dependent density functional theory to generate absorbance data for single dyes and dimer aggregates and established DNA base-dependence of dye orientation control using super-resolution spectroscopy and microscopy.[88,89]

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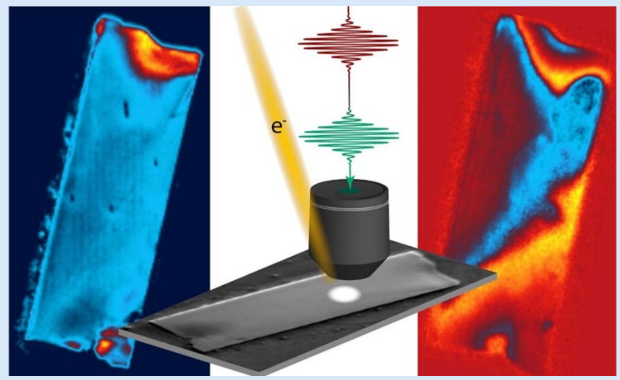
84 https://www.fhwa.dot.gov/publications/research/ear/22025/22025.pdf
85 https://doi.org/10.1021/acs.jpcb.1c07436
86 https://science.osti.gov/bes/Highlights/2022/BES-2022-02-b
87 https://doi.org/10.1126/scirobotics.abn5459
88 https://doi.org/10.1038/s42004-021-00456-8
89 https://doi.org/10.1021/acs.jpcb.1c04517

Understanding the properties and performance of perovskite devices. Researchers at Los Alamos National Laboratory, with support from DOE and in collaboration with other U.S. and international scientists, examined the performance properties of 2D perovskites under ambient conditions, finding that they can be as efficient as their 3D counterparts, which are unstable under ambient conditions. These researchers discovered shallow defects or "trap states" in Ruddlesden-Popper (RP) 2D layered perovskites that can help the charge transport over a greater distance than previously believed to be possible in a 2D quantum-confined system. This discovery implies that the carrier transport in RP perovskites can be as efficient as 3D devices, and may enable the development of RP perovskite devices that are both efficient and environmentally stable.[90] This research could lead to improved solar power and LED devices.

Understanding how defects in nanoscale crystals affect performance of photovoltaics

Lead halide perovskites have enormous promise as light absorbers in next-generation photovoltaic (PV) devices. A key challenge has been understanding the reasons why electron transport varies so widely in these materials. University researchers funded by DOE/BES (with additional support from NSF) used two advanced microscopy techniques to learn how crystal defects in lead halide perovskite PV devices affect their performance. Electron backscattering diffraction lets scientists examine crystal quality at 100 nm scale. Ultrafast microscopy uses laser pulses 100 quadrillionths of a second long to examine how electrons move. By combining these techniques, researchers found that microscopic defects that form when the crystals are made can reduce how fast electrons move by a factor of almost 10. This work suggests that variability in the crystal quality profoundly affects the efficiency of charge carrier transport in this important class of photovoltaic materials. The research could ultimately lead to improved solar power devices to advance the clean energy economy.[91]



Two techniques—co-localized electron back scattered diffraction imaging (left) and ultrafast optical microscopy (center and right)—help determine how local structural defects affect fast electron movement within a single microscopic crystal. Image credits: Montana State University.

Advancing nanomaterials, nanofabrication, and nanomanufacturing to promote U.S. leadership in semiconductors, microelectronics, and next-generation computing and communications. Company researchers supported by DOE/AMO, in cooperation with NIST, are developing an automated manufacturing process to precisely place individual atoms (known as dopants) to make semiconductors in a 2D matrix material, typically silicon, with precision an order of magnitude greater than conventional methods. The research has opened the door for exploration of new physics: making possible finite analogs to Hubbard phase-spaces with well-behaved Hamiltonians that allow implementation of new types of analog quantum simulations.[92] In related work, researchers at NIST, in collaboration with a university, have developed a step-by-step recipe to produce single-atom transistors. Using these instructions, the NIST-led team has become only the second in the world to

90 https://doi.org/10.1016/j.chempr.2022.01.008
91 https://science.osti.gov/bes/Highlights/2020/BES-2020-12-a; figures from https://doi.org/10.1021/acs.nanolett.0c01244
92 https://www.energy.gov/sites/prod/files/2019/09/f67/Automated%20Manufacturing%20of%202D%20Atomically%20Precise%20Devices%20in%20Silicon%20Subs....pdf

construct a single-atom transistor and the first to fabricate a series of single electron transistors with atomic-scale control over the devices' geometry. The team also developed a novel technique for the crucial step of making electrical contact with the devices so they can operate as part of a circuit.[93]

NIST researchers have improved a technique to identify and count defects in transistors, the building blocks of electronic devices such as smartphones and computers.[94] NIST's new and improved method is sensitive enough for use in leading-edge technologies, and can provide an accurate assessment of defects that could otherwise impair the performance of transistors and limit the reliability of the chips in which they reside. The new, modified charge-pumping technique can detect single defects as small as the diameter of a hydrogen atom (one-tenth of a billionth of a meter) and can indicate their location in the transistor. In another project, NIST researchers demonstrated ultrafast stroboscopic measurements of the subnanometer motion of mechanical resonators used in emerging technologies such as 5G wireless communications.[95] This new capability enables essential measurements of next-generation devices for communications and ultra-fast signal analysis. Example applications include silicon oscillators for precision timing, disk resonators for gyroscopes used in inertial navigation, and narrowband microwave filters used to separate transmit/receive channels in mobile wireless technologies.

University researchers supported by NSF and an industry consortium developed a new type of magneto-electric transistor made of monolayer graphene deposited on the surface of antiferromagnetic Cr_2O_3 that generates less heat and consumes significantly less energy than typical silicon-based transistors, using spin rather than charge to store information. The design could reduce the number of transistors needed to store certain data by as much as 75%. Devices made with these transistors are non-volatile (retain stored data when power is turned off) and are capable of operation well above room temperature.[96]

To realize a new type of phase transition material for use in memristive neuromorphic computing, scientists at the Naval Research Laboratory have demonstrated for the first time nanoscale control of the metamagnetic transition in FeRh thin films using He-ion beams, and the first ultra-high-speed metamagnetic neuromorphic memristive memory element. The discovery was made by irradiating a nanoscale pattern of confined regions with energy and dose-tuned He+ ions. Nanowire devices fabricated with subsequent multistep nanopatterning were tested with ultrafast electrical pulse switching, revealing memristive memory effects. The outcome is unprecedented control of magnetic ordering and the metamagnetic transition temperature on scales conceivably beyond the superparamagnetic limit. This finding opens the door to a new metamagnetic memristive memory element for use in neuromorphic spintronics,

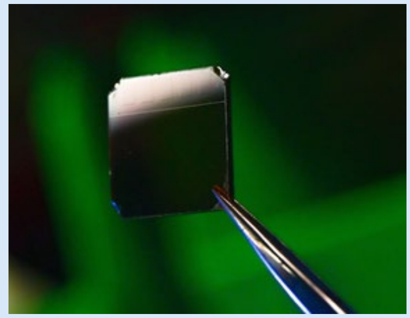
NRL scientists have been working to couple indirect gap semiconductors, such as silicon, to plasmonic nanocavities, and to realize efficient light emission in the coupled structures. The coupling is designed to exploit both the plasmonic Purcell effect and potential phonon-less plasmon emission to overcome the intrinsic poor radiative efficiency of the indirect bandgap semiconductors and turn them into viable light sources. This development addresses the last standing barrier to silicon photonics and will enable incorporation of photonic circuitry in microelectronic devices, leading to drastic improvements in computational capabilities. ONR-funded university researchers have designed a simple, compact photonic circuit that uses sound waves to rein in light. The new study demonstrates a powerful way to

93 https://www.nist.gov/news-events/news/2020/05/nist-scientists-create-new-recipe-single-atom-transistors
94 https://doi.org/10.1063/5.0081172
95 https://doi.org/10.1038/s41467-022-28223-w
96 https://doi.org/10.1002/adma.202105023

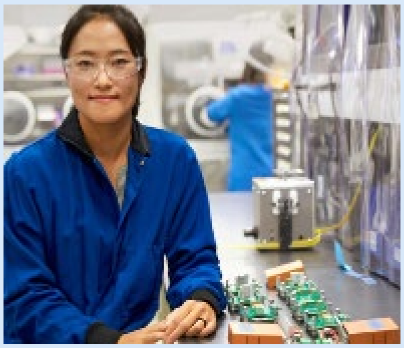
isolate or control the directionality of light. This approach to isolation outperforms all previous on-chip alternatives and is optimized for compatibility with atom-based sensors.[97]

Leveraging nanotechnology to combat climate change

Climate change is one of the biggest challenges of our time. Fighting climate change requires technical innovation, creativity, and adaptability. Nanotechnology underpins many innovative solutions that can help decrease emissions of greenhouse gasses (GHGs), increase clean energy production, enhance energy efficiency and minimize waste, and improve resiliency efforts. For example, nanotechnologies such as perovskite photovoltaics (a) and lightweight materials and coatings for wind turbines are helping increase production of carbon-free energy. Nanotechnology-powered advances in energy storage such as silicon-based batteries (b) are enabling long-term clean energy storage and distribution. Energy consumption can be reduced by adoption of nanomaterials such as graphene for lighter-weight vehicles (c), electrochromic coatings to produce better insulation materials such as smart windows (d), and advanced nanoelectronics for energy-efficient computing.



(a) Image credit: Rice University.



(b) Image credit: Todd Tankersley, courtesy of Sila.

(c) Image credit: Rice University.

Researchers are also leveraging nanotechnology to develop accurate, real-time, distributed sensors to detect an array of GHGs. Accurate detection is needed to inform mitigation and resilience efforts. Nanotechnology-enabled construction materials such as cement containing nanoscale titanium dioxide can sequester carbon from the environment and help mitigate the effects of climate change. Conversely, nanotechnology can aid in creating new resilient materials that can withstand extreme weather events. For example, super white paint containing barium sulfate nanoparticles can reflect sunlight, making buildings cooler and reducing heat islands (e).

(d) Image credit: courtesy of View, Inc.

(e) Image credit: Purdue University.

Recognizing these opportunities, the NNI announced a National Nanotechnology Challenge on climate change, Nano4EARTH, on October 7, 2022. See https://www.nano.gov/nano4EARTH.

Researchers from NIST and a university prepared and controlled a highly counterintuitive arrangement of atoms that might eventually serve as a form of durable memory in quantum information processing. This arrangement, called many-body localization, is a condition contrary to the physics of everyday life,

[97] https://doi.org/10.1038/s41566-021-00884-x

where things tend to equilibrium. This is also generally true of quantum objects unless some sort of disorder in the environment prevents them from dispersing homogenously. These results show that localization can be achieved and preserved by carefully manipulating electric and magnetic fields.

The DARPA JUMP program has demonstrated fundamental breakthroughs in electronics architecture, with design of a 3D monolithic compute-in-memory accelerator with a reconfigurable interconnect, and in new materials and electronics architecture, with design of ferroelectric transistors for in-memory computation. The 3D System on a Chip (3DSoC) program has yielded the design of carbon nanotube field-effect transistors for use in digital logic architectures. The Magnetic Miniaturized and Monolithically Integrated Components program has demonstrated dynamically controlled nonlinear magnetic films that will enable new classes of microwave devices.

Goal 2. Promote commercialization of nanotechnology R&D.

Federal investments in nanotechnology R&D have led to thousands of products in the marketplace, and today's scientific discoveries serve as the foundation for the next generation of applications, from health monitoring devices to durable infrastructure materials. The NNI fosters commercialization by sharing information, promoting access to user facilities, leveraging resources through public-private partnerships, and participating in international standards activities that are critical to commercialization. In addition to these mechanisms, NNCO has a staff member dedicated to liaison with industry and the development community by conducting outreach, sharing best practices, and suggesting collaborations as appropriate.

Supporting the entrepreneurial community. The NNI agencies and NNCO foster and support the entrepreneurial community through an array of activities such as SBIR and STTR programs (see the SBIR/STTR section above, p. 28), Innovation Corps (I-Corps™), NIH's Concept to Clinic: Commercializing Innovation Program,[98] and entrepreneurship efforts associated with the DOE National Labs (e.g., DOE/AMO's Lab Embedded Entrepreneurship program,[99] including Cyclotron Road,[100] Chain Reaction Innovations,[101] Innovation Crossroads,[102] and West Gate[103]). NNCO facilitates the Nanotechnology Entrepreneurship Network to bring new and seasoned entrepreneurs together with the people and resources available to support them.[104] This network provides a forum for entrepreneurs to share best practices for advancing nanotechnology commercialization and lessons learned along the technology development pathway.

The NSF SBIR/STTR program has an ongoing nanotechnology topic with subtopics for nanomaterials, nanomanufacturing, nanoelectronics and active nanostructures, nanotechnology for biological and medical applications, and instrumentation for nanotechnology. Other NSF programs that have been contributing to Goal 2 and supporting nanotechnology entrepreneurial activity include Grant

98 https://www.nibib.nih.gov/research-program/c3i-program
99 https://www.energy.gov/eere/amo/lab-embedded-entrepreneurship-program
100 https://cyclotronroad.lbl.gov/
101 https://chainreaction.anl.gov/
102 https://innovationcrossroads.ornl.gov/program
103 https://www.nrel.gov/innovate/west-gate.html
104 https://www.nano.gov/nanoentrepreneurshipnetwork

Opportunities for Academic Liaison with Industry (GOALI),[105] IUCRCs,[106] I-Corps,[107] Partnerships for Innovation (PFI),[108] as well as MRSECs, ERCs, CCIs, NNCI, and the Advanced Manufacturing program.

In August 2021 the first five NSF I-Corps Hubs and their participating institutions were announced,[109] expanding opportunities for entrepreneurship education and technology transfer throughout the United States. One NSF I-Corps award focused on the interactions of bent DNA molecules as amplifying sensors for the treatment of disease.[110] A PFI award focused on the production of non-invasive, nanocrystal-based systems that convert visible light into ultraviolet light *in vivo*.[111] Recent IUCRC awards with nanotechnology intersections include the Center for Solid-State Electric Power Storage,[112] the Center for High-Frequency Electronics and Circuits for Communication Systems,[113] Electronic-Photonic Integrated Circuits for Aerospace,[114] the Center for Rational Catalyst Synthesis,[115] the Center for Power Management Integration,[116] and a planning grant for a Center for Aggressive Scaling by Advanced Processes for Electronics and Photonics.[117] About 20% of active IUCRCs include nanotechnology-related projects.

The DARPA SBIR/STTR program continues to release and award topics related to nanotechnology. In 2021, DARPA made three Phase I awards and one Phase II award focused on nanomaterials and nanomanufacturing. In 2022, DARPA has made five awards (four Phase I, one Phase II), with seven awards pending (five Phase I, two Phase II), and two topics related to nanotechnology are currently in development. DARPA will continue to support technical offices that release nanotechnology topics for award as they are received. DARPA works closely with DOD (Research & Engineering) to transition nanotechnology awards to other components/agencies as well as the Office of the Secretary of Defense Transitions SBIR Technology (OTST) program to further technology development.

NIST is funding SBIR awards to help commercialize innovations from NIST laboratories. In addition, the NIST on a Chip (NOAC) program[118] is creating prototypes for a new generation of ultra-compact, inexpensive, low-power measurement tools for time and frequency, mass, force, temperature, and other key quantities, many of which are based on nanoscale measurement and device technologies. NOAC is exploring and creating robust industry and government partnerships to turn NIST innovations into commercial products that will benefit entrepreneurs and small businesses by providing access to low-cost measurement capabilities. NIST, in partnership with NIH and the Interagency Working Group for Bayh-Dole, is rebuilding the Interagency Edison (iEdison) online system for reporting inventions, streamlining administrative award management processes for Government-funded entrepreneurs and businesses.[119]

105 https://www.nsf.gov/eng/eec/goali.jsp
106 https://iucrc.nsf.gov/
107 https://www.nsf.gov/news/special_reports/i-corps/
108 https://www.nsf.gov/tip/pfi/index.jsp
109 https://www.nsf.gov/news/special_reports/i-corps/hubs.jsp
110 https://nsf.gov/awardsearch/showAward?AWD_ID=2129225
111 https://nsf.gov/awardsearch/showAward?AWD_ID=2147791
112 https://iucrc.nsf.gov/centers/center-for-solid-state-electric-power-storage-ceps/
113 https://iucrc.nsf.gov/centers/center-for-high-frequency-electronics-and-circuits-for-communication-systems-checcs/
114 https://iucrc.nsf.gov/centers/electronic-photonic-integrated-circuits-for-aerospace-epica/
115 https://www.nsf.gov/awardsearch/showAward?AWD_ID=2052817&HistoricalAwards=false
116 https://www.nsf.gov/awardsearch/showAward?AWD_ID=2052809&HistoricalAwards=false
117 https://www.nsf.gov/awardsearch/showAward?AWD_ID=2052749&HistoricalAwards=false
118 https://www.nist.gov/noac
119 https://www.nist.gov/tpo/bayh-dole/iedison-rebuild

USPTO plays a critical role in the entrepreneurial ecosystem, providing intellectual property policy advice and guidance to the Executive Branch, granting patents on nanotechnology applications that meet statutory requirements, and providing assistance on intellectual property issues to inventors and entrepreneurs.[120]

Translating bionanotechnology to benefit the healthcare value chain. Four start-up companies are using technology developed under support from the ONR Biomaterials and Bionanotechnology program. These companies have developed: (1) a biotechnological production platform that could revolutionize gene delivery and vaccine constructs for pharmaceutical and synthetic biology companies by manufacturing clinical-grade custom single-stranded DNA in gene length that specifically addresses individual needs of therapeutic applications; (2) a unique solution for massive storage and retrieval of nucleic acid samples from a range of sources including human and viral genomes to transcriptomes and digital data stored in DNA; (3) a novel reagent-based technology for ultrasensitive protein detection that offers significant benefits across the healthcare value chain; and (4) a drug discovery platform based on spatial biology.

Promoting rural economic development through development of value-added products from farms and forests. ARS researchers are developing a variety of value-added products derived from agricultural feedstocks. Ongoing and completed projects (many in collaboration with university researchers) include commercial production of nanocellulose and hemicellulose from agricultural wastes; edible nanofilms to improve safety, extend shelf-life, and improve quality of foods;[121] commercially-viable chemicals and nanoparticles for novel applications of underutilized agricultural fibers (e.g., nanocomposites);[122] and nano-aerosol-based antimicrobials for leafy vegetable disinfection.[123] Other projects cover nanoemulsions for use in bacterial decontamination of fresh produce[124] and for protein-based molecular delivery systems;[125] nanoparticle milling methods for commercial biochar composites; encapsulation of natural biopesticides into protein nanocapsules; and metal-based nanotechnology for value-added applications of cotton, including the use of nonwoven brown cotton fabric as a durable substrate for palladium nanoparticle catalysts.[126]

In 2022, P^3Nano, a public private partnership between the Forest Service and a nonprofit organization, awarded five projects to explore applications of cellulose nanomaterials. Projects include development of molded pulp products from pomace reinforced with cellulose nanofibril (CNF), cellulose nanocrystal (CNC)/polydimethylsiloxane (PDMS) hybrid moisture-selective membranes for heat recovery, CNC-protein nanocomposite coatings for perishable fruits, cellulose nanomaterials in 3D-printed building composites, and CNC as an additive for carbonated calcium silicate cement. There are five additional product development projects on scale-up of cellulose nanomaterials dispersions for tires, field trials and optimization of tree fruit protection with CNF, scale-up and formula optimization of cellulose nanomaterials for drilling fluids, scale-up and surface modification of microfibrillated cellulose for additive manufacturing, and scale-up of CNF-sizing technology for paper.

Enabling wearable health monitoring devices. University researchers at an NSF ERC are building low-power and self-powered armbands that measure electrocardiogram activity continuously without

120 See the NNI Supplement to the President's 2022 Budget, p. 36, for additional details: https://www.nano.gov/2022BudgetSupplement.
121 https://doi.org/10.21273/JASHS04972-20
122 https://doi.org/10.1007/s10570-020-03549-0
123 https://doi.org//10.1039/D0EN00814A
124 https://doi.org/10.1016/j.ijfoodmicro.2020.108936
125 https://doi.org/10.1016/j.foodhyd.2019.105177
126 https://doi.org/10.1021/acsanm.0c01303

missing a beat. These wearable devices integrate cutting-edge technologies for body heat harvesting, low-power sensing, low-power electronics, and smart textiles. The data is transmitted through low-power Bluetooth[tm] and analyzed for anomalies. This type of device can provide continuous monitoring for individuals with cardiovascular disease such as atrial fibrillation.

NASA researchers and international collaborators have developed a new colorimetric chemical sensor that leverages plasmonic gold nanoparticles for improved color contrast and enhanced sensitivity. This sensor is currently being evaluated for use in a wearable platform for astronaut health monitoring.

Advancing development and applications of nanosensors. Army/ERDC is collaborating with a university and a company to investigate new methods for integrating 2D printed nanotechnology-enabled sensors into 3D printed parts (including drones) for detection of environmental conditions (temperature, humidity). This project will enable flexibility and gas detection for greater deployability of low-cost environmental sensing in remote locations. ERDC is also working with industry and academia to develop and test the use of graphene for sensors.

A collaboration between NASA researchers and a small business has developed an approach to DNA extraction protocols to extract DNA from Mars analog soils and for the use of silicon nitride nanopores to detect the extracted DNA and corresponding characteristics.

Translating cancer diagnostics and therapeutics. The NCI Alliance for Nanotechnology in Cancer has been funding several entrepreneurial academic investigators who establish small companies to move technology developed in their laboratories to translational and commercial stages, including human clinical trials. These efforts demonstrate the application of nanomedicine in the clinic, but also the need for ongoing grant support for maturing innovative technologies towards translation.

Improving the durability and performance of infrastructure materials. Army/ERDC is researching nanoscale modification of asphalt and concrete materials, and is collaborating with university researchers to investigate nanomaterial additions to construction materials, including graphene and nanoclay, to improve mechanical properties and durability. These materials are also being used to control optoelectronic properties for a variety of future sensing and coating applications. Complementary research supported by the Federal Highway Administration has been investigating the use of nanotechnology to improve the performance, durability, and resiliency of transportation infrastructure materials. Recent projects include exploring the application of nanoscale components that can be embedded in structural elements and pavements to help gauge their interior health, and studying hydration and mechanical properties of concrete at the nanoscale. FHWA also conducted a comprehensive review of carbon nanofilaments and carbon nanotubes to develop new models aimed at making these materials better strengthening agents for bridge repairs and crack control,[127] and is investigating a follow-up research question on modeling the impact of nanowire or nanofilament orientation as reinforcement in cementitious materials on macroscale structural performance. The Forest service is working with State and local governments and the public-private partnership P^3Nano to demonstrate the use of cellulose nanocrystals as a reinforcement for concrete bridge decks.

Enabling a solar- and electric-powered future. For over a decade, an IUCRC university team funded by NSF and industry partners has been pursuing the goal of enabling the United States and the world to achieve a zero-carbon footprint by 2050 using solar energy as a resource. Nanotechnology innovations the team has developed include improving the long-term material stability of perovskite photovoltaic devices by creating, analyzing, and validating novel, low-cost stabilization strategies utilizing unique nanoscale and interfacial phenomena. The team also developed and improved the performance and

127 https://www.fhwa.dot.gov/publications/research/ear/22025/22025.pdf

stability of solar cells based on blue-emitting $CuAl_xS_y$ quantum dots that absorb a wide spectral range in the UV part of the spectrum.

NASA has been collaborating with industry and academia to design and test various system-level components that will enable the development of megawatt-class, high-power-density electric machines for electrified aircraft. Progress is being made toward increasing the technical readiness level (TRL) of components that incorporate nanomaterials. Researchers have already developed scalable processes to incorporate boron nitride nanosheets into several material systems that are of interest for components of power-dense, megawatt-scale electric motors with improved performance. Plans include material integration for component-level development. NASA researchers are also using boron nitride nanosheets as a thermally conductive, electrically insulating filler to determine how these nanosheets impact the lifetime behavior of the composite insulation in relevant application environments. This analysis is important because the lifetime of the electric motors depends on the longevity of the electrical insulation.

NASA's work complements research funded by ONR on nanoclay electrical insulation materials for power electronics that has resulted in novel nanostructured insulation materials with outstanding discharge resistance (30X better than neat epoxy resin, 15X compared to alumina nanocomposite, and with no significant erosion after lengthy testing). ONR is funding development of new ferrite-based soft nanocomposite magnetic materials and novel additive manufacturing methods, resulting in MHz switching frequency with dramatic improvements to power density. ONR is also funding basic research that may enable better lithium-ion batteries in the future: researchers are studying transition metal oxide electrodes that exhibit storage capacities beyond their theoretical values. To understand the underlying physicochemical mechanisms for this behavior, they used *in situ* magnetometry to demonstrate the existence of strong surface capacitance on metal nanoparticles. They also showed that a large number of spin-polarized electrons can be stored in the nanoparticles.[128]

ISN researchers are working to improve solid-state Li-ion batteries, which have inherent advantages due to high energy density and safety in comparison with conventional Li-ion batteries based on liquid electrolytes. The researchers are addressing a critical bottleneck: minimizing the interfacial impedances between the solid electrolyte and the active electrode materials, working to understand degradation mechanisms of this interface, and developing strategies to improve the cathode-electrolyte interface. NRL is developing 3D all-solid-state batteries comprising U.S.-sourced materials (e.g., Ag, Zn) as an energy-storage solution that delivers high energy and power in a minimal geometric footprint. A team of NRL scientists recently demonstrated conformal, thickness-controlled deposition of nanoscale polystyrene-based films on 2D planar and 3D substrates using initiated chemical vapor deposition (iCVD). These films were subsequently converted to an anion-conducting solid-state electrolyte using mass-scalable vapor- and solution-phase methods.

One of the main causes of poor Li-ion battery performance has been identified by NIST researchers, in collaboration with Sandia National Laboratories. Repeated charging and discharging, or rapid cycling, limits performance over time by increasing the battery's internal time-dependent resistance (impedance). The team used two complementary techniques—contact potential difference measurements and neutron depth profiling—to precisely determine which parts of the battery contribute most to its impedance. This work could lead to longer-lasting Li-ion batteries.

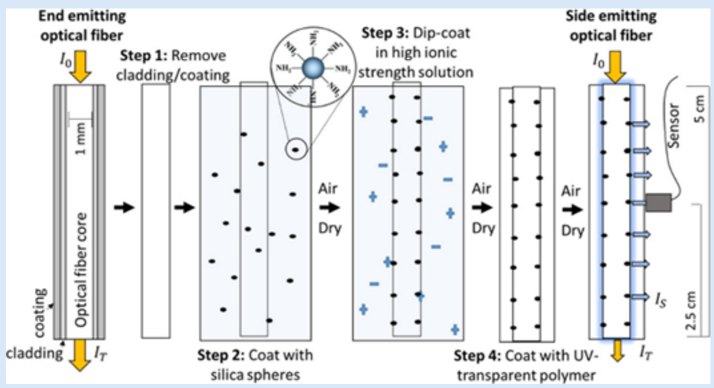
Improving catalyst synthesis for transformative applications. An IUCRC team supported by NSF and industry is demonstrating rational, scalable, bottom-up syntheses of supported single-metal and

[128] https://doi.org/10.1038/s41563-020-0756-y

bimetallic catalysts with previously unachievable control of metal nanoparticle size and metal1-metal2 interactions. For example, a team of researchers at the center has discovered an inexpensive, simple, and scalable method for preparing high-density single-atom catalysts without the need for binding sites, for applications such as fuel cells and plastics recycling. This discovery has strong industrial interest given its transformative potential in the chemical industry.

Advancing nanomanufacturing for energy efficiency. DOE/AMO nanomanufacturing projects have included the development of advanced nanocarbon-metal composites for improved energy efficiency. New composite materials consisting of graphitic carbon and metals show remarkable graphene nanoribbons that could be a mechanism for electrical conductivity increases.[129] Building on this, DOE/AMO established the Conductivity-enhanced materials for Affordable, Breakthrough, Leapfrog Electric and thermal applications (CABLE) initiative.[130] Ten CABLE Prize Stage 1 Winners, eight new CABLE SBIR/STTR Phase I winners, and five new CABLE SBIR/STTR Phase II winners were recently added to the research ecosystem on using nano-carbons and nanoscale processes to enhance conductivity.

Ensuring the quality of potable water in space



Workflow for fabricating 5 cm UV-C scattering optical fibers. End emitting fiber polymers are stripped of their cladding and coating. The fibers are dipped in silica spheres, then a high-ionic-strength coating before the addition of the UV-transparent polymer. Image credit: Arizona State University.

In support of its involvement in the NNI's water nanotechnologies interagency interest group, NASA has used its STTR program to explore applications of nanotechnology to maintain and monitor potable water quality for future human space missions. A novel method of modifying the shape, size, and surface chemistry of silica nanoparticles used to coat optical fibers improved the side emission of germicidal UV-C light by more than 100 times. The coated fiber is then overlaid with a UV-C transparent polymer that protects the fiber, prevents nanoparticle release into water, and allows germicidal light to enter the water.[131] Passivation approaches to extend the lifetime of silver nanoparticle antimicrobial coatings have been investigated to inhibit biofilm growth within potable water piping, enabling sustained biofouling control.[132] Carbon nanotubes functionalized with recognition molecules as part of microelectronic sensor platforms are being investigated for monitoring biocidal levels of silver in spacecraft potable water. Other water quality monitoring concepts under development include a microfluidic colorimetric sensor using functionalized metal nanoparticles with analyte-specific ligands,[133] use of a solid-state silicon nitride nanopore chip for inorganic and organic multianalyte monitoring,[134] and fiber optic surface-enhanced Raman spectroscopy utilizing silver nanoparticles, including microfluidic pre-concentrators incorporating nanoporous silica-rich sorbents to improve detection.[135]

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129 https://www.energy.gov/sites/prod/files/2019/10/f67/Fabrication%20of%20Nanocarbon%20Metal%20Composites.pdf
130 https://www.energy.gov/eere/amo/articles/energy-department-launches-new-manufacturing-prize-improved-conductors-support
131 https://doi.org/10.1021/acs.est.9b01958 (figure source)
132 https://doi.org/10.1016/j.colsurfb.2022.112562
133 https://sbir.nasa.gov/SBIR/abstracts/21/sttr/phase1/STTR-21-1-T6.06-1513.html
134 https://doi.org/10.1063/1.5138210
135 https://sbir.nasa.gov/SBIR/abstracts/20/sttr/phase2/STTR-20-2-T6.06-4928.html

Developing and exploiting nanomaterials for advanced nuclear power applications. DOE/NE has a number of projects ongoing or nearing completion to explore the applications of nanomaterials to nuclear power applications. Examples include understanding the effect of neutron irradiation on microstructure and mechanical properties of nanocrystalline nickel and developing irradiation-resistant nanostructured thermoelectric materials and devices for in-pile power harvesting and sensing. NE is also working to improve understanding of swelling-related embrittlement of irradiated AISI316 stainless steel on the nanometer length scale and is developing nanodispersion-strengthened metallic composites with enhanced neutron irradiation tolerance. The effects of radiation on optical fiber sensor-fused smart alloy parts with graded alloy composition manufactured by additive manufacturing processes are under investigation. Efforts to confirm and understand the enhanced irradiation tolerance of nuclear-application steels via nanostructuring are underway using innovative manufacturing techniques. NE also has research focused on understanding nanostructured material behavior and nanostructural changes in materials that are important to innovative reactors and nuclear energy applications.

Maturing structural aerospace nanomaterials. NASA is supporting companies through Phase 3 SBIR contracts to mature technologies to manufacture lightweight, high-strength structural nanomaterials. These include composite overwrap pressure vessels, high-strength CNT structural composites, carbon and CNT preforms, and carbon-carbon composite structures for space applications.

Transforming electronics manufacturing and applications. AFRL worked with industry and university partners to develop a novel method using laser treatment of an amorphous MoS_2 thin-film precursor sputtered material to fabricate complete electronic devices by controlling the laser patterning, which imparts insulating, conducting, and semiconductor properties to the circuit elements as needed. The team varied the incident visible laser intensity and raster-scanned the thin-film a-MoS_2 sample at different speeds for microscale control of crystallization and reaction kinetics, transforming select regions of the film into MoO_2, MoO_3, and 2H-MoS_2 phases, exhibiting conducting, insulating, and semiconducting properties. Electrical devices (e.g., resistor, capacitor, chemical sensor) have been laser-written directly within the precursor film, demonstrating a transformative approach for the fabrication of electronic circuitry.[136]

The DARPA Atomic-Photonic Integration program has demonstrated ultra-broadband, low-noise microresonator frequency combs (microcombs) that provide new opportunities for optical frequency synthesis and optical atomic clocks. The Precise Robust Inertial Guidance for Munitions program has developed nanotechnology-enabled next-generation inertial measurement units (IMUs) that are being applied to unmanned vehicles.

Developing vaccines effective against multiple variants of COVID-19 and other diseases. Following from the work at NIH, BARDA, FDA, and DOD previously reported on LNP-encapsulated mRNA vaccines to combat the COVID-19 pandemic,[137] several efforts are now underway to develop “pan-coronavirus vaccines” that will be effective against multiple variants of SARS-CoV-2 and other related viruses. In one such effort, researchers at the Walter Reed Army Institute of Research developed a spike ferritin nanoparticle (SpFN) COVID-19 vaccine that not only elicits a potent immune response but may also provide broad protection against SARS-CoV-2 variants of concern (VoCs) as well as other coronaviruses. Human clinical trials began in April 2021.[138] Complementary work at NIH/NIAID evaluated an alphavirus-based self-amplifying RNA vaccine expressing spike proteins from the SARS-CoV-2 Alpha variant and

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[136] https://doi.org/10.1016/j.mattod.2020.09.036

[137] See NNI Supplement to the President’s 2022 Budget, p. 37: https://www.nano.gov/sites/default/files/pub_resource/NNI-FY22-Budget-Supplement.pdf

[138] https://mrdc.health.mil/index.cfm/media/news_releases/2021/pan_coronavirus_vaccine_development_strategy

recent VoCs delivered *in vivo* via a lipid inorganic nanoparticle. Animal trials showed that vaccination induced potent neutralizing titers against each homologous VoC and reduced protection against heterologous challenges, but with significantly reduced shedding of infectious virus.[139] These results demonstrate that this vaccine platform elicits significant protective immunity against SARS-CoV-2 variants and support continued development of this platform.

NIAID-supported researchers also developed a novel customizable nanoparticle platform that enables researchers to quickly and robustly create candidate vaccines for a variety of pathogen-caused diseases, including SARS-CoV-2, influenza, RSV, and hepatitis C. Vaccines for SARS-CoV-2 developed using this method have completed Phase 3 clinical trials in Korea; a flu nanoparticle vaccine was co-developed by researchers at the NIAID Vaccine Research Center (VRC) and is in Phase 1 clinical trials at the VRC.

NIAID continues to progress in its efforts to develop a universal flu vaccine.[140] VRC researchers investigated a 24-mer self-assembling influenza ferritin nanoparticle vaccine in a clinical trial and found it to be safe, well-tolerated, and immunogenic in adults. The vaccine also induced broadly cross-reactive immune responses targeting the conserved part of the influenza hemagglutinin protein, providing a proof-of-concept for the ferritin nanoparticle-based vaccine platform.[141] VRC scientists and academic colleagues have also designed a self-assembling two-component nanoparticle vaccine that performed as well as or better than the commercial vaccine in eliciting antibody responses matched to the vaccine hemagglutinin (HA) components and that was far better in eliciting protective antibody responses to viruses that were not included in the vaccine.[142] In related work, researchers have developed a version of the nanoparticle vaccine that displays four different HAs from seasonal influenza subtypes; a clinical trial for this vaccine began in 2021 at the VRC.[143]

Driving effective medical countermeasures and pandemic preparedness with public-private partnerships. A novel vaccine adjuvant developed with NIAID funding contributed to the success of a highly efficacious COVID-19 vaccine called COVAXIN, which received Emergency Use Listing by the World Health Organization in 2021 and has been licensed in 23 countries as of October 2022. The adjuvant used, Alhydroxiquim-II, was discovered and tested in the laboratory by a U.S.-based biotech company with support exclusively from the NIAID Adjuvant Development Program.[144] The adjuvant comprises a small molecule, which travels to lymph nodes, where it activates two cellular receptors. These receptors, TLR7 and TLR8, play a vital role in the immune response to viruses. Alhydroxiquim-II is the first adjuvant in an authorized vaccine against an infectious disease to activate TLR7 and TLR8. The collaboration between the U.S. company making the adjuvant and the Indian company that makes COVAXIN was initiated during a 2019 meeting in India coordinated by the NIAID Office of Global Research under the auspices of NIAID's Indo-U.S. Vaccine Action Program.[145]

Empowering future vaccines and immunotherapies with nanotechnology-based adjuvants. ISN researchers are working on nanotechnology-based approaches that target vaccine adjuvants or immunomodulators to lymph nodes, with the capacity to enhance both the potency and safety of vaccines by focusing adjuvant activity in tissues where immune responses are initiated and avoiding

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139 https://doi.org/10.7554/eLife.75537
140 See NNI Supplement to the President's 2021 Budget, p. 29: https://www.nano.gov/sites/default/files/pub_resource/NNI-FY21-Budget-Supplement.pdf
141 https://pubmed.ncbi.nlm.nih.gov/35115706/, https://pubmed.ncbi.nlm.nih.gov/35115707/
142 https://pubmed.ncbi.nlm.nih.gov/33762730/
143 https://www.niaid.nih.gov/news-events/nih-launches-clinical-trial-universal-influenza-vaccine-candidate
144 https://www.niaid.nih.gov/news-events/adjuvant-developed-nih-funding-enhances-efficacy-indias-covid-19-vaccine
145 https://www.niaid.nih.gov/research/indo-us-vaccine-action-program-overview

systemic exposure. They are exploring the use of organic nanoparticles formed through the self-assembly of the glycolipid saponin, the Toll-like receptor agonist monosphosphoryl lipid A, cholesterol, and phospholipids to activate innate immune pathways to augment subunit vaccines. This novel adjuvant, SMNP (saponin/MPLA nanoparticles), induces superior immune responses compared to a broad range of experimental and clinical vaccine adjuvants in mice, and also elicits neutralizing antibody responses against HIV immunogens in non-human primates. Recent work has shown that SMNP affects antigen trafficking through mast cells, which causes enhanced lymph flow.[146] This is the first demonstration of a vaccine adjuvant that functions through effects on lymphatic vessels and lymph flow. With support from NIH, efforts have begun to translate this vaccine adjuvant into a first-in-humans clinical trial. NIAID continues to support the discovery and development of nanoparticulate adjuvant formulations through several dedicated programs, and several alternative combinations based on TLR4 agonists and saponin adjuvants are currently being developed through the NIAID Adjuvant Mimic (SBIR contract) program, such as combinations of synthetic derivatives of MPL, and novel saponins that address reactogenicity, chemical instability, and shortage of the commonly used QS-21 saponin.

Assuring regulatory clarity for nanotechnology-enabled drugs and medical devices. FDA is conducting outreach to applicants in the early stages of the development of products that incorporate nanotechnology. These efforts seek to educate industry regarding the regulations governing the products regulated by each FDA center and clarify how the inclusion of nanotechnology impacts regulation of these products. For example, at FDA's Center for Drug Evaluation and Research (CDER), the Office of Generic Drugs supports research related to the development of complex generic products that contain nanotechnology, as part of its Generic Drug User Fee Amendments science and research program. This research supports the development of novel empirical and modeling methodologies to characterize nanotechnology in complex drug products, to evaluate how critical attributes of the nanotechnology can influence the performance of these complex drug products, and to support decisions about appropriate ways to regulate them. Through various types of scientific communications and regulatory guidances, the outcomes of this research help generic drug manufacturers characterize and understand the nanotechnology in brand name reference products and develop complex generic drug products that contain nanotechnology. The commercialization of these nanotechnology-containing generic products enhances patient access to affordable, high-quality, safe, and effective medicines, and secures a diversified supply of important medicines, mitigating the risk of drug shortages.

In support of commercialization of nanotechnology, in April 2022 CDER and the FDA Center for Biologics Evaluation and Research (CBER) finalized a Guidance for Industry, Drug Products, Including Biological Products that Contain Nanomaterials.[147] This guidance explains the principles and specific considerations for developing drugs containing nanomaterials, including via abbreviated pathways. The guidance emphasizes the need to adequately characterize the nanomaterial, understand the nanomaterial's intended use and application, and understand how the nanomaterial attributes relate to product quality, patient safety, and efficacy.

Recognizing that adopting innovative approaches to manufacturing (including drug products containing nanomaterials) may present both technical and regulatory challenges, CDER is also exploring the limits of manufacturing processes for nanomaterials, such as liposomes and lipid nanoparticles, to facilitate future development of improved therapeutics and vaccines.

Supporting standards development. NNI agencies support standards activities to streamline development, regulatory approval, and market acceptance of nanotechnology-enabled products. NIST

[146] https://pubmed.ncbi.nlm.nih.gov/34860581/
[147] https://www.fda.gov/media/157812/download

leads and participates in several organizations where voluntary consensus nanotechnology standards are being developed. U.S. leadership and participation in the development of international standards ensures that the United States can shape the strategic and technical direction of nanotechnology development everywhere. The expertise that NIST scientists contribute to the development of these consensus standards helps ensure that the resulting standards are technically robust, timely, and fit-for-purpose. NIST experts' leadership and engagement in pre-standardization activities such as those being conducted under the Versailles Project on Advanced Materials and Standards (VAMAS) helps accelerate the development of consensus standards by leveraging the outcomes of the round-robin testing efforts within VAMAS activities to inform the development of consensus standards. Many NSET agencies participate in standards development activities, including ASTM International's Committee E56 on Nanotechnology, chaired by NIST. NIST also participates with other Federal agencies, industry, academic, and nongovernmental organizations on the U.S. Technical Advisory Group (TAG) (accredited by ANSI), chaired by NIOSH. The TAG represents the United States at ISO TC 229, Nanotechnologies, and is responsible for formulating positions and proposals on behalf of the United States regarding ISO nanotechnology standardization activities. NIST staff members also lead nanotechnology-related efforts in Technical Committee 113 of the International Electrotechnical Commission.

The FDA Nanotechnology Standards Subcommittee is assisting in international standards development by identifying standards needs and supporting the review of documentary standards. In calendar year 2021, this subcommittee reviewed and provided comments on 28 draft standards that came through for review through ISO and ASTM. FDA's Center for Devices and Radiological Health (CDRH) continues to assess the relevance of published consensus nanotechnology standards to the current submissions review. In 2021, CDRH added one ASTM E56 standard and one ISO TC 229 standard to its list of recognized standards for nanotechnology, bringing the total number of standards recognized and adopted for review of nanomaterials in medical devices to 20. These documentary standards support industry and regulators by facilitating premarket review of product submissions. The critical scientific data and information generated from this research and standards development work is used in capacity building and helps the agency ensure the safety of FDA-regulated products containing nanomaterials.

An ongoing multi-year interagency agreement (IAA) between NIH/NIDCR and NIST aims to accelerate the development of measurement methods, standards, and reference nanomaterial-based composites for the dental and biomaterials communities. The IAA covers three thrust areas: (1) Measurement Methods for Next-Generation Dental Restoratives, (2) High-Throughput Screening of Selectivity Elements for Intraoral Electrochemical Sensors, and (3) Predictive Early-Stage Biocompatibility Testing of Dental Materials. An initial workshop held in November 2021 (in cooperation with CPSC, NIH/NIEHS, and the Army Public Health Center) resulted in the publication of a report outlining a framework for enabling high-quality measurements in support of alternative testing methods (e.g., *in vitro*, *in chemico*, and computational approaches) that can potentially be used to reduce animal testing.[148] Outcomes from this IAA are expected to mitigate challenges in regulatory science, and, in turn, help to accelerate the lab-to-human and lab-to-market translation of novel nanotechnologies in dentistry.

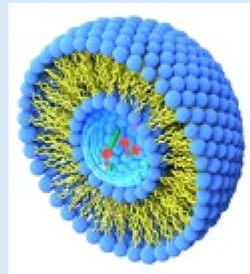
Several other NNI participating agencies are active in nanotechnology-related standards activities. For example, Forest Service experts lead the revision of cellulose nanomaterials terms and definition project in ISO TC 229 and the cellulose nanomaterials working group in ISO TC6 (pulp, board, paper). CPSC staff and partners are engaged in voluntary standards activities to create validated methods for quantifying and characterizing exposures from nanotechnology-enabled products, including an ISO project evaluating the release of nanomaterials from treated wood. CPSC is also leading efforts to

148 https://doi.org/10.14573/altex.2205081

develop standard methods for testing and assessing particle releases from 3D printers, and is working with a safety standards organization to develop a guide for the safe use of materials and overall 3D printer use. It has completed a project with ERDC and a university to develop new approaches and a device for abrading CNT-containing 3D printed materials, and developed a model to predict the impact of the material matrix on the potential health effects of the matrix-bound nanomaterials.

Standards protect public health and facilitate commercialization of nanotechnology-enabled drug products

The FDA/NCTR Nanocore developed three test method standards through the ASTM E56 Committee on Nanotechnology for lipid quantitation in liposomal drug products. These standards were finalized in 2022, after three years of collaborative consensus work across multiple groups of the stakeholder community, with support from the NIH/NIEHS Division of Translational Toxicology.[149] The NCTR Nanocore team conducted research supporting collaborative consensus development for these standards, with support from the FDA Nanotechnology Task Force, FDA product centers, stakeholders, and subject matter experts from other U.S. Government agencies, academia, and industry. These internationally recognized test method standards are an invaluable resource for both FDA and industry to protect and promote public health, and to increase predictability, streamline pre-market review, and facilitate market entry of nanotechnology-enabled drug products.



Artist's depiction of a liposome. Image credit: Shutterstock.

Goal 3. Provide the infrastructure to sustainably support nanotechnology research, development, and deployment.

The physical equipment, digital models, simulations, and data that make up the research infrastructure are essential for all of the NNI goals. The need for expensive, specialized tools remains a key requirement for much of nanotechnology R&D. One distinguishing feature of the NNI is the user facilities that provide researchers and developers with access to the critically enabling tools required to create, characterize, and understand nanomaterials and nanotechnology-enabled components, devices, and systems. NNI agencies support advances in tool development, establishment of facilities, and creation and dissemination of cyber resources through mechanisms such as individual grants, collaborative centers, and networks of user facilities.

Sustaining and leveraging the NNI user facilities and other infrastructure. NSF support for the NNCI user facilities is providing researchers from academia, small and large companies, and government with access to leading-edge fabrication and characterization tools, instrumentation, and staff expertise within all disciplines of nanoscale science, engineering, and technology. In the last full year of available data, NNCI served 11,242 unique users who performed a significant part of their experimental work at NNCI facilities. Of these, 2,793 (24.8%) were external users: 1,619 from industry (70% of those were small companies), 964 from external academic institutions, 162 from government, and 48 from other countries.[150] NCN is advancing nanoscience and nanotechnology modeling, simulation, and networking through nanoHUB.org, which has become a successful, scientific end-to-end cloud-computing environment, hosting over 3,000 resources for research, collaboration, teaching, learning, and publishing. NCN served two million users in 2020, in multiple domains. The Cyberinfrastructure for

[149] https://www.fda.gov/about-fda/nctr-publications/nctr-research-highlights?utm_medium=email&utm_source=govdelivery#June16

[150] NNCI Coordinating Office Annual Report (Year 6, April 2021–March 2022): https://nnci.net/nnci-annual-report

Sustained Scientific Innovation solicitation[151] is contributing to nanotechnology data infrastructure, software advances, and high-throughput computation. The NSF Nanosystems Engineering Research Center for Nanomanufacturing Systems for Mobile Computing and Energy Technologies (NASCENT) has been creating and validating scalable, cost-effective nanomanufacturing infrastructure. For example, NASCENT activities include designing scalable precision roll-to-roll nanomanufacturing equipment integrated with in-line sensing and nanometrology, developing methods for transforming system data into optimal process control and yield enhancement, and collaborating with industry partners to deploy nanomanufacturing technologies broadly. In addition, NSF supports academic research infrastructure at more than 500 universities through its core programs and its support for research, education, and technology transfer centers.

DOE operates five Nanoscale Science Research Centers that are Office of Science national scientific user facilities, which provide open access to leading-edge synthesis, fabrication, characterization, and computational tools along with scientific expertise for interdisciplinary research at the nanoscale. In 2021, these centers provided access to over 3,300 scientific user projects from academia, industry, and government, based on a peer-reviewed proposal system. The NSRCs provide critical capabilities to researchers from across the nanotechnology spectrum, including areas relevant to microelectronics, quantum information sciences (QIS), and clean energy. In 2021, for example, research associated with NSRCs to advance microelectronics included optimizing materials performance and imaging capabilities, and investigating defect-engineered electronic structures for tuning of excited-state decay pathways.[152] In QIS, new 2D materials were investigated, including discovery of higher-magnitude interface superconductivity and theoretical demonstration of space-time crystalline order in unconventional superconductors.[153] Specialized techniques such as automated scanning probe microscopy and machine-learning algorithm-based principles were used to understand the structural and electronic changes in correlated materials.[154] NSRC research in clean energy has recently focused on battery materials, including sodium- and lithium-ion-based cathodes for optimizing tunnel structures, mechanical integrity, and recycling.[155] Additionally, there was research in efficient catalytic materials for electrochemical conversion of nitrogen to ammonia and photoelectrochemical water splitting.[156]

NIST has been providing another key element in the network of NNI nanotechnology user facilities and research centers. User facilities include the NCNR, the CNST NanoFab, the Boulder Microfabrication Facility, and the NIST beamlines at NSLS-II.[157] In addition, NIST-sponsors the Center for Hierarchical Materials Design (CHiMaD), a center of excellence for advanced materials research focusing on developing the next generation of computational tools, databases, and experimental techniques to enable the accelerated design of novel materials and their integration to industry, one of the primary goals of the MGI. CHiMaD is a Chicago-based consortium of universities, Argonne National Laboratory, a small business, and a professional society.

The National Cancer Institute, in collaboration with NIST and FDA, established the Nanotechnology Characterization Laboratory to perform preclinical efficacy and toxicity testing of nanoparticles. NCL

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151 https://www.nsf.gov/pubs/2021/nsf21617/nsf21617.htm

152 https://doi.org/10.1038/s41586-020-03092-9, https://doi.org/10.1063/5.0065164, https://doi.org/10.1021/jacs.1c07795

153 https://doi.org/10.1103/PhysRevB.104.195302, https://doi.org/10.1126/science.aba5511, https://doi.org/10.1038/s41467-021-26132-y

154 https://doi.org/10.1126/science.abg1874, https://doi.org/10.1038/s41467-020-20342-6

155 https://doi.org/10.1021/acsenergylett.1c01868, https://doi.org/10.1016/j.joule.2021.09.005, https://doi.org/10.1038/s41467-021-26290-z, https://doi.org/10.1021/acsaem.1c01598

156 https://doi.org/10.1021/acsnano.1c07771, https://doi.org/10.1021/acsami.1c19623

157 See PCA 3 section, above (p. 20) for details.

serves as a national resource and knowledge base for all cancer researchers to facilitate the regulatory review of nanotechnologies intended for cancer therapies and diagnostics. To-date, in its 16 years of operation, NCL has characterized 450 different nanomaterials with a wide range of nanotechnologies and therapeutic loads; established 250 collaborations with academia, industry, and government labs; published over 200 peer-reviewed publications covering nanoparticle characterization, immunotoxicity, and safety; and established over 70 standardized protocols for various nanoparticles assays. Seventeen NCL collaborators reached clinical trials with the aid of data produced at NCL. In the effort to help combat the global COVID-19 pandemic, NCL accepts applications for novel nanomaterials used for prevention and treatment of COVID-19.

Developing new tools to advance nanotechnology and nanomanufacturing. A team of staff and users at the DOE Molecular Foundry NSRC developed a method to optimize encapsulated transition metal dichalcogenides (TMDs) for cathodoluminescence (CL) imaging that will enable the study of buried nanoscale structures in beam-sensitive materials such as quantum dot superlattices or biological samples. They focused on monolayer 2D $MoSe_2$ encapsulated in a hexagonal boron nitride layer, optimizing both spatial resolution and brightness of TMD emission by tuning the hBN thickness below 100 nm. Hyperspectral CL maps resolved spectrally distinct nanoscale features below diffusion-limited spatial resolution.[158]

University researchers supported by DOE/AMO developed a new tool for 3D atomically precise sculpting—“mechanosynthesis”—a novel manufacturing approach where atomically perfect structures are created by directly moving atoms. This tool gently transfers atoms sequentially in 3D through a combination of mechanics and special chemistry. The initial goal was to fabricate an atomically precise scanning probe microscope (SPM) tip by sequentially removing defect atoms via externally controlled 3D movement of the tip around a molecular tool anchored on a surface. The project has achieved formation of activated, surface-bound reactants by SPM, demonstrated the ability to use the selected reactant as a probe to image the SPM, and successfully removed atoms from the tip through reactant-driven abstraction.[159]

DOE/AMO-supported university researchers, in partnership with a company and NIST, have done ground-breaking work to develop scanning probe microscopy (scanning tunneling microscopy and atomic force microscopy) instrumentation for high-throughput atomically precise (AP) manufacturing, initially for applications in quantum computing but also for ultra-energy-efficient microelectronics manufacturing (including failure detection) and metrology. The objective of this research project is to speed up and improve STM control so large arrays of STMs can quickly and precisely fabricate commercial quantities of AP materials, features, and devices. The team has secured numerous patents arising from this work. These innovations may also lead to a wide variety of other energy-saving applications, including diffraction arrays with unprecedented optical performance, molecule-specific membrane filters, catalytic surfaces, and improved boiling interfaces for heat transfer.[160]

NRL is developing new tools to measure the flow of protons in biology through the use of nanoscale devices. Electron flow in biology is useful in many ways, including power in biological fuel cells. The role of protons during those electronic measurements is not well understood. Palladium can be used similar to an electrode, but to move protons, in this work known as a “protode.” Proton movement can then be monitored, sometimes simultaneously with electronic signal, in biological materials like chitosan, reflectin, prefoldin, and some bacteria species. Learning how to measure and control proton movement

158 https://doi.org/10.1039/D1NR08082B

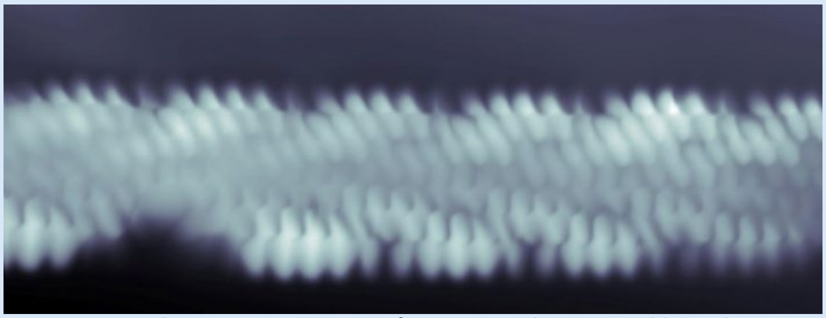
159 https://stage.energy.gov/sites/prod/files/2019/10/f67/A%20Radical%20Tool%20for%203D%20Atomically%20Precise%20Sculpting_0.pdf

160 https://www.osti.gov/servlets/purl/1902882

enables scientists to better interact with biology, communicate in biology's native language, and may eventually lead to prosthetics that are better performing and better tolerated by the individual.

Creating new techniques to understand and harness the magnetic properties of graphene nanoribbons for spintronic devices

Slicing graphene along the edge of its honeycomb lattice creates one-dimensional zigzag graphene strips, or nanoribbons, with exotic magnetic properties. Researchers at Lawrence Berkeley National Laboratory and a university are working towards harnessing these properties to enable the development of carbon-based spintronic devices for high-speed, low-power data storage and information processing technologies by encoding data through electron spin instead of charge.[161] *To overcome the problem that zigzag nanoribbons are highly reactive, the team developed a method to stabilize the edges of graphene nanoribbons and directly measure their unique magnetic properties by substituting some of the carbon atoms along the ribbon's zigzag edges with nitrogen atoms, allowing them to tune the local electronic structure without disrupting the magnetic properties. This also enabled the development of a scanning probe microscopy technique for measuring the material's local magnetism at the atomic scale.*[162]

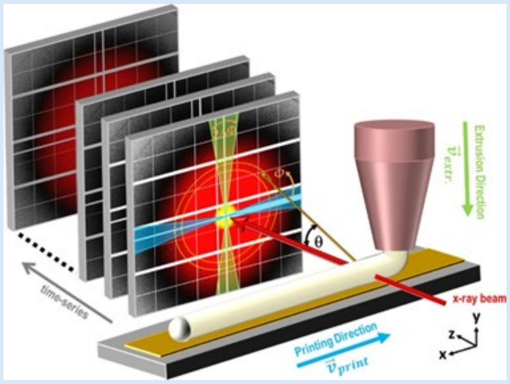

Scanning tunneling microscopy image of a zigzag graphene nanoribbon. The image captures an area of 27 nm^2. Image credit: Felix Fischer/Berkeley Lab.

University scientists combined a silicon-based topological photonic crystal with an atomic monolayer of hBN. The topological features of the photonic crystal are coupled to the lattice vibrations of the hBN through the formation of phonon-polaritons. Funneling of helical infrared phonons along arbitrary pathways and across sharp bends provides the possibility of realizing directional heat dissipation along topologically resilient heat sinks. This could enable advances in Raman spectroscopy as well as infrared spectroscopy.[163] This research was supported by ONR.

AFRL scientists, in cooperation with Oak Ridge National Laboratory, developed an advanced scanning probe microscopy approach for simultaneous nanoscale mapping of surface potential, dielectric, and piezoelectric properties of ferroelectric surfaces. For quantitatively mapping electromechanical properties, they used interferometric displacement-sensing piezoresponse force microscopy, which measures the effective piezoelectric coefficient free of background artifacts such as the cantilever body electrostatics. The dielectric and surface electrochemical properties were captured during Gmode electrostatic force microscopy/Kelvin probe force microscopy operated in the lift mode.[164] They have also developed and refined techniques for combining piezoresponse force microscopy with density functional theory and machine learning to gain new insights into a variety of other important electronic materials and alloys.

161 https://newscenter.lbl.gov/2021/12/22/graphene-nanoribbons-electronic/
162 https://www.nature.com/articles/s41586-021-04201-y
163 https://doi.org/10.1126/science.abj5488
164 https://doi.org/10.1063/5.0078034

AFRL partnership uses NNI infrastructure and AI for quality control



Real-time x-ray scanning of a composite extruded during additive manufacturing. Image credit: AFRL.

AFRL, in partnership with a university-based high energy synchrotron facility, developed and validated innovative measurement tools to probe the structure of high-performance nanocomposites in real time. High-resolution x-ray microbeam scanning and phase contrast imaging techniques were used in an emerging low-cost manufacturing process. In collaboration with DOD contractors, the partnership established routines that led to unprecedented speed and accuracy in detection of process bottlenecks, e.g., during additive manufacturing of carbon fiber- or CNT-filled high-performance polymers. Coupled with machine learning tools, processing flaws were detected and visualized nearly instantaneously, compared to months of analysis previously. University researchers also developed automated, AI-driven materials discovery routines using the beamline's real-time probing techniques. Potential applications of this technique range from flexible electronics to aerospace, agile manufacturing, and specialty nanomaterials.[165]

Developing improved analytical and test methods for timely regulatory review of nanotechnology-enabled products. FDA's Office of Regulatory Affairs (ORA) works with FDA product centers to conduct collaborative research to develop analytical methods for the characterization of nanomaterials in FDA-regulated products. Such methods will enable FDA to identify potential risks associated with such products through pre- and post-market oversight and determine problems that can affect product safety. Additionally, these regulated methods will provide guidance to sponsors/reviewers for future product approvals and authorizations. For example, FDA is developing advanced *in vitro* test methods to evaluate medical devices that incorporate nanomaterials with various physicochemical properties and medical applications. Due to the complexity of biological evaluation of nanomaterials in medical devices and limitations of existing *in vitro* and *in vivo* models, the development and utilization of dynamic *in vitro* models have the potential to simulate the complex physiological environment and provide more clinically relevant biological responses. One investigation is exploring development and application of a dynamic, *in vitro* vascular model using physiologically relevant flow conditions to evaluate biological responses to nanomaterials applied intravascularly for various medical device applications, including diagnostics and therapeutics. The results demonstrate that toxicity of nanoparticles on the dynamic human vascular endothelial model is inflammation-related and dependent on nanomaterial size, concentration, and flow rate. These findings highlight the complexity of nanotoxicity, the importance of physiologically relevant conditions in nanotoxicity evaluation, and the potential application of microphysiological systems in safety evaluation of nanomaterials.

FDA/ORA recruits and trains research fellows in development and validation of advanced analytical methods based on FDA, the United States Pharmacopeia (USP), and International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for characterization of nanomaterial constituents of FDA-regulated products. These methods can be used for pre- and post-market regulatory testing.

165 http://doi.org/10.1021/acs.langmuir.9b00766 (image source)

Goal 4. Engage the Public and Expand the Nanotechnology Workforce.

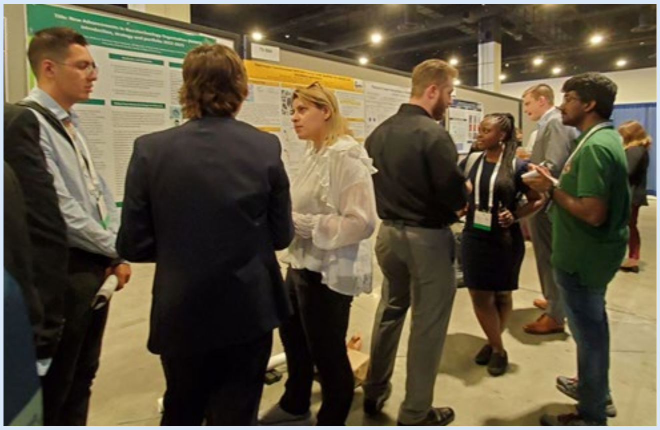
Nanotechnology innovation relies on STEM talent and a highly skilled workforce for every aspect of the R&D continuum. Thousands of students are trained every year in NNI-supported nanotechnology user facilities and research centers. In addition, there are targeted curriculum development efforts and internship programs, and NNI-funded research centers partner with community colleges to promote training of the technical workforce.

NNCO works with NNI participating agencies, university-based student groups, and teachers organizations to conduct public outreach and help inspire students to learn about the unique opportunities that nanotechnology presents, and thus to pursue STEM careers.[166] There are particular efforts to promote opportunities and access to resources for people in traditionally underserved communities.

Leveraging infrastructure for education and outreach. NNI user facilities and research centers play an important educational role. For example, in the most recent reporting period, NNCI centers trained 4,400 first-time new users.[167]. In another example, an NSF ERC offered a mini-course providing a hands-on introduction to using deep learning architectures for the processing of biosignals using nanosensors. The topic was relevant to the center's research and also contributed to its goal of training graduates who are creative, adaptive, competitive, life-long learners equipped to make significant impact in their fields.

NextTech Student Network: STEM retention through shared scientific passion

The NextTech Student Network[168] is a group of student-run clubs at universities and colleges across the country that share a passion for nanotechnology and other emerging technologies. The network shares resources, webinars, and professional development opportunities, and organizes the annual Student Leaders Conference (SLC). The SLC provides an opportunity for students from across the network to meet each other in person, share best practices, present their research and/or club activities, and meet and talk with a wide array of professionals from academia, industry, and government. At the 2022 SLC, the students organized two panel sessions to discuss careers and moving research into action. Students had the opportunity to hear the career pathways of professionals from diverse backgrounds who spoke about entrepreneurship, different careers within academia, how to scale up research ideas, and the role of Government scientists. The SLC is co-located with a major international technology and innovation conference, which maximizes the learning and networking opportunities for the students. This enriching experience has provided students with funding for their clubs' activities, internship and fellowship opportunities, and one-on-one meetings with potential graduate school advisors and/or employers.



Students presenting their research and NextTech club activities at the June 2022 Student Leaders Conference. Image credit: NNCO.

166 See examples of NNCO outreach activities illustrated on the inside back cover of this report, and the sidebar in this section of the report.

167 NNCI Coordinating Office Annual Report (Year 6, April 2021–March 2022): https://nnci.net/nnci-annual-report

168 https://nexttechnetwork.org/

Training students through immersive educational experiences. In 2021, the NSF INTERN program supported about 65 student NS&E-related internships in industry and government labs, including at AFRL. FDA's Center for Food Safety and Applied Nutrition (CFSAN) has supported and expanded the nanotechnology workforce by sponsoring post-doctoral and other trainees through opportunities such as the Oak Ridge Institute for Science and Education (ORISE) Training Fellowship Program and other cooperative agreements. These ORISE trainees work closely with their designated CFSAN mentors to carry out cutting-edge nanotechnology research in CFSAN laboratories.

The future of aviation will involve developing cleaner and safer technologies for next-generation human and cargo air transportation. One way that NASA supports this demand is through its University Leadership Initiative project, Atoms-to-Aircraft-to-Spacecraft (A2A), where university students and faculty are using design, multiscale modeling, and advanced fabrication tools to rapidly manufacture high-temperature, CNT-filled thermoplastic composites for urban air mobility vehicle structures. NASA's Space Technology Graduate Research Opportunity (NSTGRO) program is sponsoring rising scientists and engineers who are developing innovative space technologies to support NASA missions. Several nanotechnology-related awards involve virtual prototyping of multifunctional boron nitride nanostructures and composites in extreme environments, functionalizing nanoporous organic frameworks for separation applications, and using nanophotonic lithium niobate to develop advanced visible to mid-infrared integrated coherent sources. Under the NSTGRO program, fellows receive annual training by NASA research collaborators through a Visiting Technologist Experience in the fellow's relevant technology area.

Assuring access of underrepresented groups to nanotechnology education and workforce development. NNI participating agencies have numerous programs that support inclusion, diversity, equity, and access to STEM education and workforce opportunities for people from communities that have been historically left behind. NSF is supporting activities to increase diversity and equity by inclusion and access for minorities, women, and persons with disabilities interested in nanoscale science and engineering, and for broad geographical representation in all 50 states.[169]

DHS's Summer Research Teams (SRT) program funds early career faculty and up to two students from minority-serving institutions to conduct research at one of the twelve DHS Centers of Excellence (COEs) and their partners for ten weeks during the summer.[170] In one recent year, an SRT team developed a low-cost, handheld sulfur emission detection device enabled by nanotechnology for U.S. Coast Guard marine inspectors, in collaboration with the Maritime Security Center COE. The prototype sensor platform can be used to efficiently and effectively monitor compliance and enforce the International Maritime Organization's global cap on vessel sulfur emissions. The device has been recommended for an invention disclosure and potential patent by the COE's technology commercialization office.[171] Another SRT team conducted research in the summer of 2021 on processing and characterization of photosensitive composite nanofibers for oil spill cleanup,[172] and is doing follow-on work using composite nanofiber mats loaded with porous carbon in 2022.[173]

169 See NNI Supplement to the Presidents 2022 Budget, pp. 48-49 for additional details: https://www.nano.gov/sites/default/files/pub_resource/NNI-FY22-Budget-Supplement.pdf

170 https://www.dhs.gov/homeland-security-careers/summer-research-team-program

171 https://www.dhs.gov/science-and-technology/news/2021/05/20/feature-article-cultivating-talented-diverse-rd-workforce-of-the-future

172 https://www.dhs.gov/science-and-technology/news/2021/05/17/news-release-st-selects-2021-minority-serving-institutions-summer-research-teams

173 https://www.dhs.gov/science-and-technology/news/2022/02/28/st-awards-funding-minority-serving-institutions-advance-summer-research-projects

START: Building community college student technical capabilities via universities partnering with industry

Image credit: NSF.

An innovative partnership between the cross-NSF IUCRC and ATE programs called START (Skills Training in Advanced Research and Technology) places and trains community college faculty and students in cutting-edge industry-driven research projects with breakthrough potential that drive industry innovation in targeted sectors of the economy.[174] *Community colleges are often the first step in the higher education of students from marginalized and underserved groups due to their low cost, evening courses, and locations close to students. By focusing on community colleges, START supports national efforts to broaden the participation of students from groups that are underrepresented in science and technology. In START, faculty, graduate students, and postdocs at IUCRCs and their industrial advisory board members include, train, and mentor community college students and faculty. Working alongside and closely with each other, the university, community college, and industry partners learn from each other and benefit from the ideas, skills, and perspectives each brings to the table. Initiated in 2021, START now involves active participation of 23 IUCRC universities, 38 community college faculty members, and 124 community college students. About 20% of active IUCRCs include nanotechnology-related projects.*[175]

Engaging with the public. The NNI recognizes that public trust in nanoscience and technology is critical for the potential of nanotechnology innovations to be realized. NNCO produces three podcast series—*Stories from the NNI*, *Nanotechnology Entrepreneurship Network*, and *NanoMatters*—that target researchers, entrepreneurs, and the general public.[176] NNCO also organizes public webinars to share research, technological, and environmental health and safety information with the public. NNI agencies participate in celebrating National Nanotechnology Day (NND)[177] as an effort to spread the exciting world of nanotechnology with a broader audience. For example, FDA and DOE/AMO have both been active participants in NND.

FDA/CFSAN has been actively participating in both domestic and international meetings to educate and inform the public of the center's regulatory perspective on and scientific efforts regarding nanotechnology and related issues. For instance, in 2021, several presentations pertaining to food ingredients and food contact substances containing nanomaterials and micro- and nanoplastics in food were given at meetings organized by various educational institutions and scientific organizations.

Goal 5. Ensure the responsible development of nanotechnology.

The responsible development of nanotechnology has been an integral part and goal of the NNI since its launch. The 2021 NNI Strategic Plan articulates an expanded framework for responsible development that includes long-standing considerations such as understanding ELSI and the nanoEHS implications of nanotechnology development. This new framework further embraces additional concepts, including

[174] https://www.nsf.gov/pubs/2021/nsf21013/nsf21013.jsp
[175] Photo taken from: https://uidp.org/wp-content/uploads/2021/05/UIDP-NSF-START-Slides.pdf.
[176] https://www.nano.gov/podcast
[177] https://www.nano.gov/nationalnanotechnologyday

an emphasis on inclusion, diversity, equity, and access and the responsible conduct of research. These efforts support the other NNI goals by helping ensure the integrity of nanotechnology R&D and fostering public confidence and regulatory certainty.

Promoting inclusion, diversity, equity, and access. NNI participating agencies have a number of programs in place to promote diversity and assure access to the benefits of nanotechnology to all Americans, in particular access to high-paying careers in science and engineering by persons from historically under-represented communities. For example, NSF's Broadening Participation in STEM Initiative includes a variety of approaches to build STEM education and research capacity in under-served communities, catalyze new areas of STEM research, and develop strategic partnerships and alliances; the website includes a portal to a number of specific NSF programs targeting those communities.[178] At the DOE Office of Science, diversity, equity, and inclusion are considered key to advancing the U.S. research and scientific innovation enterprise. Stewardship and promotion of diverse and inclusive workplaces that value and celebrate a diversity of people, ideas, cultures, and educational backgrounds is foundational to the office's mission.[179] In October 2021, OSTP announced the Advancing Equity in Science & Technology Ideation Challenge to gather ideas, insights, and recommendations from the public on how to guarantee that all Americans can fully participate in, and contribute to, science and technology.[180] These valuable programs and resources are actively being promoted to the nanotechnology community in support of the NNI's focus on IDEA.

Developing novel approaches to detecting and understanding biological interactions of engineered nanomaterials. An NSF-funded university researcher developed a multi-element inductively coupled plasma mass spectrometry approach for detecting engineered titanium nanoparticles in the environment. The low contribution of sunscreen Ti nanoparticles and their rapid dilution upon release suggested minimal ecotoxicological impacts to surface waters during recreational activities such as tubing and swimming.[181] In another NSF-funded project, a Faculty Early Career Development (CAREER) program awardee developed a multispectral imaging approach to investigate how single human cells interact with and process engineered nanomaterials. Single-walled carbon nanotube sensors with unique physical, optical, and electronic properties were actively internalized by cells and localized to specific organelles that function to "eat" and digest extracellular biomolecules. From there, the nanosensors simultaneously reported their progression through the intracellular environment and the resulting changes to their physical condition.[182]

EPA scientists recently reviewed the major types and applications of quantum dots (QDs) and their potential environmental exposures, fates, and adverse effects on organisms. Potential effects were analyzed in relation to QD structure, function, synthesis methods, and exposures. They identified data gaps in QD exposure and ecological effects to inform future research.[183] EPA also teamed with university researchers to demonstrate a novel method for quantitative detection of engineered nanomaterials in contaminated soil by extracting $Ce0_2$ nanoparticles using tetrasodium pyrophosphate aqueous solution and then characterizing the extracts via single-particle inductively coupled plasma mass spectroscopy.[184]

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178 https://beta.nsf.gov/funding/initiatives/broadening-participation
179 https://www.energy.gov/science/diversity-equity-inclusion
180 https://www.challenge.gov/?challenge=ostp-time-is-now
181 https://nsf.gov/awardsearch/showAward?AWD_ID=1512695
182 https://nsf.gov/awardsearch/showAward?AWD_ID=1844536
183 https://doi.org/10.1039/D1EN00712B
184 https://doi.org/10.1021/acs.jafc.0c06343

Leveraging interagency nanoEHS expertise. NNI agencies have collaborated on nanoEHS research through interagency agreements, data sharing, and joint planning of research priorities facilitated by discussions in the NSET Subcommittee's Nanotechnology Environmental and Health Implications (NEHI) Working Group. For example, the NIH/NIEHS Division of Translational Toxicology is collaborating with NIOSH to allow for the evaluation of industry-wide exposure assessment of worker exposure to graphene and other two-dimensional nanomaterials, and with FDA/NCTR to support development of standards and analytical approaches for characterization and quantitation of nanomaterials, including characterization of real-world samples containing nanoplastics. These studies will facilitate appropriate planning for studies to assess the potential human health impact of exposure to nanoplastics.

Given CPSC's size and budget, partnering has been a key element in achieving mission success. It has collaborated with NIST, NIOSH, EPA, DOD, and other NNI participating agencies to address various potential EHS implications of nanomaterials and nanotechnologies in consumer products. Since 2003, these collaborative activities have produced more than 70 reports and publications, in addition to voluntary standards resulting from CPSC-funded research that addresses nanomaterial hazards in consumer products. In 2021, five publications evaluated the influence of polymer additives on gas-phase emissions from 3D printer filaments, characterized the influence of carbon nanotube content on abraded products and microplastic particle production, and evaluated the safer use of 3D printers in educational settings. In addition, CPSC supported the U.S. participant in an international research collaboration, completed in 2021, to understand how silver nanowire properties (e.g., dimensions) influence human and environmental toxicity and to develop mechanisms to minimize potential hazards. Three publications highlight the collaboration on silver nanowire synthesis and characterization, human and environmental toxicity testing, and silver nanowire release from products and recycling.[185] Results of this work could help emerging nanowire-enabled products to be safer and more sustainable for people and the environment.

Leveraging and coordinating internationally on nanoEHS research and regulatory science. NNCO and NNI participating agencies have established strong relationships with governments and organizations around the world to coordinate with and leverage nanoEHS research and regulatory activities in other countries and international fora. The U.S.-European Union (EU) nanoEHS Communities of Research (CORs) are an exemplar of such engagement. The CORs meet virtually throughout the year to discuss scientific advances and needs, identify collaborative activities, and plan an annual workshop, the most recent of which was hosted by the EU in June 2022.[186] FDA has played a key role in organizing the periodic Global Summit on Regulatory Science, which has included nanotechnology or nanoplastics as a theme on several occasions.[187] NNI agencies participate in OECD, ISO, ASTM, and other international fora that address nanotechnology-related standards and regulatory issues. For example, EPA leads the U.S. delegation to the OECD Working Party on Manufactured Nanomaterials, which seeks an internationally harmonized approach to delivering high-quality hazard, exposure, and risk assessments for manufactured nanomaterials through the development of work products such as guidance documents and test guidelines, including new approach methods (NAMs) such as *in vitro* methods.[188]

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185 https://doi.org/10.1073/pnas.1820041116, https://doi.org/10.1039/C8EN00890F, https://doi.org/10.1016/j.impact.2020.100217

186 U.S.-EU NanoEHS Communities of Research, 2022 NanoEHS COR Workshop, https://us-eu.org/2022-nanoehs-cor-workshop/; accessed 23 May 2022

187 https://www.fda.gov/about-fda/science-research-nctr/global-summit-regulatory-science

188 https://www.oecd.org/science/nanosafety/publications-series-safety-manufactured-nanomaterials.htm

Finding alternatives to animal testing

As the diversity of products and processes incorporating ENMs continues to grow, new approaches to environmental, health, and safety testing are required. Member agencies within the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM),[189] with participation from NNI representatives, have reviewed the guidance and interests of participating agencies in new approach methodologies (NAMs) such as in vitro *or* in chemico *test methods for ENMs.[190] ICCVAM's work is a step towards enhancing the technical reproducibility and biological relevance of NAMs in ENM safety testing to protect both human and environmental health and reduce or eliminate the need for testing in animals. Nanomaterials are being designed with promising properties that are furthering NAMs by facilitating improvements to high-throughput screening platforms and microfluidic techniques. For example, nanomaterials-enabled organs-on-a-chip, a microfluidic technique, could be used to test and monitor a wide range of biologically-relevant responses to potential new drugs.[191]*

Image credit: EPA, Dec. 2021 NAMs Workplan.

UNITED STATES ICCVAM Advancing Alternatives to Animal Testing

Image credit: ICCVAM.

Ensuring the safety and efficacy of nanotechnology-enabled vaccines. FDA's ongoing nanotechnology efforts span multiple FDA product and research centers. One particularly significant area in recent years has been the response to the COVID-19 pandemic, where the promise of nanotechnology for public health was unambiguously demonstrated,[192] and where FDA played a key role in the careful and expedited review for safety and efficacy of diagnostics, therapeutics, and vaccines.

Over the last several years, CBER has been reviewing a new class of vaccines against viral infectious diseases that uses lipid nanoparticles, based on a novel technology to produce the viral protein against which immune responses are mounted, encapsulating messenger RNA to synthesize the viral protein antigen inside the cells of the vaccine recipient. An advance that made this vaccine approach possible was the development of suitable LNPs that not only protect the mRNA from degradation, but also allow the release of the mRNA from the LNP once inside cells. The body then raises immune responses against the viral protein. Because CBER had reviewed earlier versions of mRNA vaccines that were directed against other infectious diseases (e.g., Zika), there was considerable experience evaluating the safety and manufacturing of this class of vaccine, which facilitated the safe and expeditious introduction of LNP mRNA vaccines against COVID-19. Based on the demonstrated safety and effectiveness of these vaccines, FDA authorized for emergency use the first two mRNA COVID-19 vaccines in December 2020. The first mRNA vaccine was licensed in August 2021 and the second in January 2022. From the success of these COVID-19 vaccines, it is clear that LNP-encapsulated mRNA will continue to be explored as a vaccine platform against many infectious diseases, including new COVID variants and other pandemic and

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189 https://ntp.niehs.nih.gov/whatwestudy/niceatm/iccvam/index.html
190 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9115850/
191 https://doi.org/10.1016/j.tips.2020.11.009
192 See NNI Supplement to the President's 2022 Budget, p. 37, for details: https://www.nano.gov/sites/default/files/pub_resource/NNI-FY22-Budget-Supplement.pdf

seasonal influenza viruses, Nipah and Hendra viruses, Lassa virus, and other coronaviruses. In addition to vaccines, FDA is evaluating and facilitating the development of other uses of mRNA technology.

Assuring and improving food safety, sustainability, and security. FDA's Center for Food Safety and Applied Nutrition has been conducting research on the use of nanotechnology in food ingredients and food contact substances, e.g., exploring the potential for consumers to be exposed to engineered nanomaterials from nanotechnology-enabled food contact materials. Information about nanoparticle migration and transformation within food systems improves the center's ability to make recommendations to manufacturers about this emerging technology and will help its regulatory scientists make informed decisions when reviewing future submissions to its food contact notification program. In addition, CFSAN is also actively conducting research on certain regulated food additives that may have incidental presence of nanoparticles. This type of work ensures that current data are available for the safety assessment of food additives that may contain nanoparticles. Furthermore, CFSAN is involved in research and development of nanotechnology-enabled sensors for contaminants, biological toxins, and pathogens in food products, which help improve FDA's ability to respond rapidly to foodborne disease outbreaks and other emerging threats to human and animal health.

Complementing CFSAN's work, a multistate research committee supported by NIFA conducted a literature survey on micro-/nanoplastics in agricultural production and food. The published article[193] provides a broad overview of recent literature on the presence and impact of microplastic (1 μm to 5 mm in size) and nanoplastic (1 to 1000 nm in size) particles across the agricultural and food supply chain and discusses methods and technologies for the detection and characterization of these particles. It also makes recommendations for future research and infrastructure needs, including novel analytical methods and sensors, high-precision lab analysis combined with rapid onsite screening, and data hosting and curation.

A team of EPA, university, and State government scientists, with partial support from NIFA, conducted a review of nanotechnology-enabled pesticides (e.g., nanomaterial-encapsulated pesticidal active ingredients that can be used for controlled and targeted delivery) to assess their potential for supporting sustainable agriculture and improving global food security. The researchers analyzed the properties of nanopesticides in controlling agricultural pests for crop enhancement compared them with conventional pesticides. The preliminary conclusions showed higher efficacy of nanopesticides against target organisms and lower toxicity to non-target organisms. The study assessed other potential benefits, including enhanced adhesion to foliage, improved crop yield and quality, and the ability to mitigate stresses such as heat, drought, and salinity. The team also noted some remaining uncertainties and recommended further research.[194]

Complementary efforts by ARS and the Forest Service are assessing the use of nanocellulose and other nanomaterials and nanotechnologies to improve food safety, quality, and shelf life (see Goal 2 section above, p. 45, for details).

Understanding and mitigating potential impacts of nanotechnology in the workplace. As nanomaterials and nanotechnology-enabled products make their way into commerce, NNI agencies work with a variety of partners to fully understand the potential health and safety impacts. NIOSH plays a key role in addressing the impacts of nanotechnology in occupational settings. NIOSH researchers develop hazard and safety assessments of key classes of engineered nanomaterials that are, or are likely to be, entering into commerce. NIOSH has performed "real-world" evaluations of hazard and risk

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193 https://doi.org/10.1007/s00216-022-04069-5

194 https://doi.org/10.1038/s41565-022-01082-8

represented by various nanomaterials through their life cycles, including the characterization of aerosols generated in spray coating of paints, sealants, and disinfectants. Environmental chambers are being used to evaluate sanding, sawing, and cutting of nanotechnology-enabled polymer composites and construction materials, as well as sanding of coated surfaces, in a controlled environment. NIOSH also has collaborated with over 20 national and international universities and numerous industrial partners in the characterization of toxicological effects of pulmonary and dermal exposure to a wide range of industrially relevant nanoparticles and nanotechnology-enabled materials.

Agencies participating in the NNI are also actively engaging with industry to share nanoEHS knowledge and best practices. NIOSH has published an extensive library of documents offering guidance and best practices in the safe use of nanotechnology in the workplace.[195] NIOSH field research teams visit nanomaterials producers and users and conduct industrial hygiene evaluations. NIOSH has used its research findings to develop guidance documents to protect workers from occupational injury and illness. NIOSH has participated in numerous webinars and in-person seminars reaching hundreds of workers, providing them with information on how to work safely with nanoscale and other advanced materials.

NIOSH is collaborating with industry to conduct voluntary *in situ* assessments of workplace exposures, evaluating workplace processes and developing methods to identify and quantify worker nanomaterial exposures. Collaborating organizations gain access to NIOSH's expertise in nanomaterial characterization and exposure-control technology. NIOSH field research teams visit nanomaterials producers and users, including additive manufacturing and 3D printing facilities.

NIOSH is also working with industry to develop an exposure registry that currently consists of ~585 workers across the United States who have been exposed to carbon nanotubes and nanofibers in the workplace. This registry will form the base of a longitudinal study that will evaluate the early health effects of exposure to carbon nanotubes or nanofibers among workers exposed to these engineered nanomaterials.

Understanding and addressing the implications of incidental nanoplastics. NNI agencies are collaborating to address emerging issues associated with micro- and nanoplastics in the environment. An informal interagency nanoplastics interest group, chaired by FDA and including over 20 participating agencies, has been meeting periodically since 2019 to facilitate cooperation among and leveraging of agencies' R&D and regulatory efforts on this emerging topic. Interest group participants are also collaborating internationally. In 2021, NIST and the EU Joint Research Centre held an internal workshop to coordinate efforts in measurement and metrology for identifying and characterizing micro- and nanoplastics. The group also played a key role in proposing and helping to organize the December 2021 APEC Workshop on Nanoplastics in Marine Debris.[196]

Examples of recent research include work by an EPA team to demonstrate the use of molecular tools such as metabarcoding to assess the types of organisms present in marine sediment by using genetic material extracted from the sediment. The team studied changes in the composition of organisms as a result of nanoplastics contamination to understand how plastic particles can adversely affect marine ecosystems and what types of organisms are most sensitive to nanoplastics.[197] NCEH and ATSDR have reviewed data in the literature for quantifying human exposures to micro- and nanoplastics and

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195 See https://www.cdc.gov/niosh/topics/nanotech/default.html. See also the NNI Supplement to the President's 2022 Budget, p. 51: https://www.nano.gov/sites/default/files/pub_resource/NNI-FY22-Budget-Supplement.pdf.

196 http://nanoplasticworkshop.org/

197 https://cfpub.epa.gov/si/si_public_record_report.cfm?dirEntryId=354774&Lab=ORM

potential health risks, and presented the results at two 2021 national conferences.[198] ARS scientists have published a review of micro- and nanoplastic-induced cellular toxicity in mammals, assessing cytotoxicity of micro-/nanoplastics as a function of cell type; the effects of particle size, dose, charge, exposure time, and additives; and the implications of oxidative stress and membrane damage for cell viability.[199] NIST and Army/ERDC scientists collaborated with European university researchers to review standardized methods for assessing potential environmental hazards of engineered nanomaterials and how those methods might be applied to assessment of micro- and nanoplastics. They outlined a strategy for leveraging OECD guidance documents developed for ENMs to improve the quality of the data generated for micro- and nanoplastics.[200] Another NIST team developed a technique for isolating, measuring, and identifying sub-100 nm plastic particles in water, using ultra-high purity water solutions exposed to plastic samples. The resulting suspensions were atomized and injected into a flowing air stream and rapidly dried to isolate the plastic particles. A variety of particle counting and characterization methods were then used to enable sample identification, quantification, and comparability for a range of nanomaterials suspended in water.[201]

Investigating potential hazards of 3D printer emissions. EPA, NIOSH, CPSC, NIST, and other NNI participating agencies are collaborating in this area, including on research to characterize the release and transformation of nanomaterials from 3D printer emissions.[202] In December 2021, the agencies convened an internal coordination meeting to discuss research results so far and potential future collaborations. Many studies have focused on fused filament fabrication (FFF) 3D printers and other technologies utilizing polymer feedstocks. Future research will likely investigate metal additive manufacturing technologies and materials, as well as potential hazards of the use of 3D printers by consumers and small businesses. For example, an EPA research team recently investigated human exposure to metals in FFF printers aimed at consumer markets.[203]

Developing and curating databases of nanoEHS research findings. EPA has published a peer-reviewed journal article documenting its efforts on the NaKnowBase project,[204] and has posted an initial publicly available version of the database on the EPA website.[205] EPA is working in coordination with other Federal agencies to promote interoperability of NaKnowBase between NNI participating agencies. This complements long-standing efforts by NIH/NCI's caNanoLab to facilitate data sharing in the cancer nanotechnology research community to expedite and validate the safety and efficacy of nanomaterials used in biomedicine. CaNanoLab supports the annotation of nanomaterials with composition information, and physico-chemical, *in vitro*, and *in vivo* characterizations, providing access to samples, protocols, and publications from NCI/NCL, the NCI Alliance for Nanotechnology in Cancer, and the broader biomedical nanotechnology community.[206] In 2021, caNanoLab compiled and curated 83 samples, 36 publications, and 1 new protocol to its database. OSHA, NIOSH, NIEHS, and NSF have also been supporting nanoEHS database efforts. These and other NNI nanoEHS informatics activities are coordinated through an informal interagency interest group.

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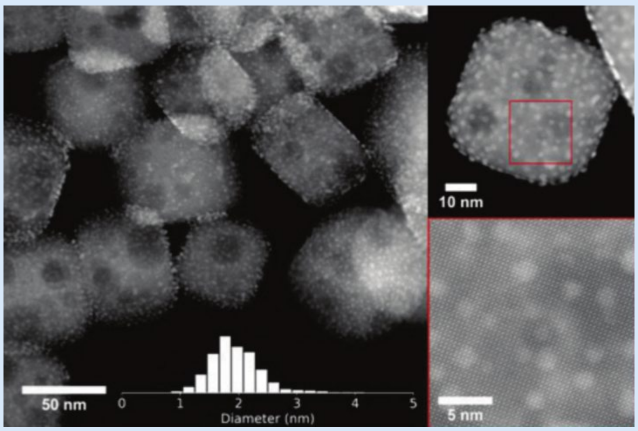
198 https://doi.org/10.1016/j.scitotenv.2020.144010
199 https://doi.org/10.1016/j.scitotenv.2020.142518
200 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9029759/
201 https://doi.org/10.1021/acs.est.1c06768
202 See the NNI Supplement to the President's 2022 Budget, p. 52, for details: https://www.nano.gov/sites/default/files/pub_resource/NNI-FY22-Budget-Supplement.pdf.
203 https://doi.org/10.1016/j.scitotenv.2021.152622
204 https://doi.org/10.1038/s41597-021-01098-0
205 https://gaftp.epa.gov/EPADataCommons/ORD/NaKnowBase/
206 https://cananolab.nci.nih.gov/caNanoLab/

Addressing science and technology challenges to a sustainable plastics economy

NNI agencies are pursuing a variety of basic and applied nanotechnology research in pursuit of the goal of making plastics more sustainable. For example, a DOE-wide effort, the Plastics Innovation Challenge, is exploring approaches to encourage increased recycling, develop methods for "upcycling" plastic waste into useful products, and develop new plastics that are recyclable by design.[207] *One project has developed a method for upcycling polystyrene plastic into a reusable adhesive with a rare combination of strength and ductility, using boronic esters to couple the polystyrene with silica nanoparticles. This opens pathways for a new class of tough adhesives that can bear heavy loads, tolerate extreme stress and heat, and reversibly bond to surfaces such as glass and metals.*[208]

NIST's Circular Economy Program supports a model in which the atoms and molecules that are the building blocks of products repeatedly cycle within the economy and retain their value.[209] *The initial focus of this program is on innovative technologies for recycling/upcycling plastics and polymers.*



Electron micrograph of platinum nanoparticles deposited on $SrTiO_3$ by atomic layer deposition for the selective hydrogenolysis of high-density polyethylene to waxes. Image credit: Argonne National Laboratory.

The NSF Emerging Frontiers in Research and Innovation (EFRI) program, partnering with DOE's Bioenergy Technologies Office and NIST, supported 17 projects under the Engineering the Elimination of End-of-Life Plastic Waste EFRI topic.[210] *Research themes, many of which leverage nanotechnology, range from synthetic biology for mixed plastic degradation and reutilization, to plasma-assisted hydrogenolysis of waste plastics, and rationally designed enzyme-containing plastics. Additional projects are supported under NSF's Critical Aspects of Sustainability*[211] *and Environmental Convergence Opportunities in Chemical, Bioengineering, Environmental, and Transport Systems*[212] *programs.*

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207 https://www.energy.gov/plastics-innovation-challenge/plastics-innovation-challenge
208 https://doi.org/10.1126/sciadv.abk2451
209 https://www.nist.gov/circular-economy
210 https://www.nsf.gov/news/news_summ.jsp?cntn_id=303230
211 https://beta.nsf.gov/funding/opportunities/critical-aspects-sustainability-cas
212 https://beta.nsf.gov/funding/opportunities/environmental-convergence-opportunities-chemical-bioengineering-environmental

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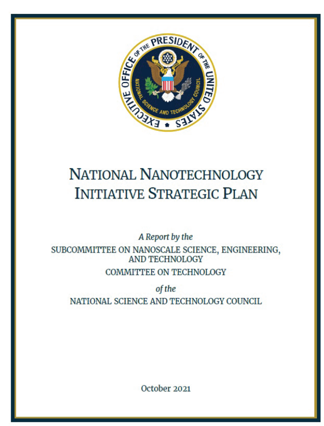
Examples of Engagement with the NNI Community

The NNI Family of Podcasts

National Nanotechnology Day

NanoEducators Quarterly Forum

Student Leaders Conference



NATIONAL NANOTECHNOLOGY INITIATIVE STRATEGIC PLAN

A Report by the
SUBCOMMITTEE ON NANOSCALE SCIENCE, ENGINEERING, AND TECHNOLOGY
COMMITTEE ON TECHNOLOGY
of the
NATIONAL SCIENCE AND TECHNOLOGY COUNCIL

October 2021

Strategic Plan

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