This is a chapter from the NIDDK’s Annual Report. The full Report includes highlights of research on these and many other areas across the NIDDK’s mission and is available at: www.niddk.nih.gov/about-niddk/strategic-plans-reports/niddk-recent-advances-emerging-opportunities
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Health equity means that everyone has opportunities to live long, healthy, productive lives—no matter who they are, how they identify, or where they live. NIDDK is committed to advancing health equity by supporting research to enable all communities affected by NIDDK diseases and conditions to thrive. To that end, as highlighted in this chapter, a new report outlines research recommendations from the NIDDK Working Group of Council on Health Disparities and Health Equity Research. These recommendations complement other NIDDK strategic planning efforts with high-impact opportunities and equity-focused principles to advance the Institute’s mission and to pursue pathways to health for all.
Cross-Cutting Science

Medical advances are not usually achieved in great, intuitive leaps. More often, new prevention strategies, treatments, and cures result from a long, gradual accumulation of knowledge from years of scientific research. Insights into fundamental biological building blocks and processes—genes, the proteins they encode, the inner workings of cells, and the ways cells communicate with each other—can have broad and far-reaching implications. Indeed, many significant advances in our understanding and treatment of disease can be traced to laboratory studies whose relevance to health could not have been fully known or appreciated at the time they were conducted.

NIDDK’s research mission is broad and includes some of the most chronic, common, consequential, and costly diseases and conditions affecting people in the United States. Many of these diseases and conditions are associated with health disparities, and innovative new ways to combat these disparities are needed to promote health equity. Additionally, while scientific talent is well represented in people of all backgrounds, opportunity is not. Thus, NIDDK strives today to promote a steady and diverse pool of talented investigators who can make tomorrow’s innovative breakthroughs.

Described in this chapter are examples of NIDDK efforts to overcome these critical challenges through research and scientific workforce development. In these ways and others, NIDDK works toward its goal of building a pathway to health for all.

DELVING INTO DNA STRUCTURE AND REPAIR

Insights Into Cellular Regulation of Chromosome “Caps”: Researchers identified a key regulator of human telomere length with potential implications for diseases and disorders of telomere biology as well as broadly for human health. Telomeres are sequences of DNA found on the ends of chromosomes—the structures in which DNA is organized within a cell. When a cell divides, a bit of DNA sequence from the chromosome end is lost naturally. This shortening is counteracted by a protein that synthesizes new telomeric DNA, so telomeres act as a “cap” to protect the critical genetic information from degradation and keep chromosomes stable. Natural telomere shortening is a hallmark of aging and is associated with increased incidence of disease, including age-related diseases, and poorer outcomes. In addition, disruption of telomere maintenance (such as through inherited genetic alterations) can cause a number of conditions including bone marrow failure, cardiovascular disease, lung disease, liver cirrhosis, and cancer. Bone marrow failure syndromes, also known as telomere biology disorders, lead to impaired blood production. Therefore, understanding the regulation of human telomere length is vital to developing treatments for a variety of diseases and disorders and promoting human health.

Using an approach that allowed them to screen a large number of genes for effects on telomere length in human cells in the laboratory, scientists identified the molecule thymidine (one of the building blocks [bases] of DNA), and genes that affect levels of thymidine, as important regulators. When genes predicted to promote production of thymidine were turned off, the scientists observed short telomeres in the cells. Conversely, when genes predicted to decrease levels of thymidine, such as the thymidine-degrading gene \textit{SAMHD1}, were turned off, they found longer telomeres. Interestingly, this regulation appeared to be specific and unique to thymidine; altering the levels of the other three DNA bases did not have the same effect. The researchers also demonstrated similar effects when supplementing the cells with thymidine or treating the cells with small molecules that decreased thymidine production. These results suggest a novel and key role for thymidine in regulating telomere length.

Identification of a key regulator of telomere length reveals a new potential strategy to treat a variety of diseases and disorders.
Given that some current therapies for cancer and other diseases alter production of molecules like thymidine, the scientists tested whether a similar approach might have potential to treat telomere biology disorders. They found that supplementation of thymidine in cells from people with different telomere biology disorders promoted telomere lengthening, suggesting the possibility of a new therapeutic strategy. This promising approach will need to be studied in animals, including humans, to determine whether the effects are similar to those observed in the laboratory and to develop further this exciting advance.


Molecular Structures Provide Insight Into Key Players in DNA Damage Repair: New research from scientists in NIDDK’s Intramural Research Program has provided useful insight into the function of proteins involved in repair of damaged DNA. DNA is one of the basic building blocks of life, providing the genetic code to make every cell in our bodies. We encounter environments and situations daily that can damage our DNA, such as exposure to certain chemicals, UV radiation, and errors cells make in replicating their DNA. Additionally, some chemotherapeutic drugs intentionally damage DNA to effectively kill cancer cells. If left unchecked, DNA damage itself can lead to genetic alterations that can contribute to the development of several inheritable disorders and even some cancers. Therefore, the body uses different strategies to repair the various types of DNA damage, including one strategy called nucleotide excision repair (NER). NER involves several different proteins within the cell working together to recognize and cut out the damaged area of DNA. Understanding the details of this process could unlock new ways to treat or prevent some disorders and cancers.

Using synthetic mimics of different types of DNA damage, together with proteins known to be involved in NER in humans, the researchers created detailed molecular images of the protein interactions with the damaged DNA site. Detection of damaged DNA in the cell can occur through two different pathways: through stalling of the process by which cells create RNA copies of DNA, or through recognition by a group of proteins that scan the genome for potential damage. These proteins are called xeroderma pigmentosum complementation group C, or XPC, named after one type of condition in which NER is compromised, resulting in extreme sensitivity to UV light. After recognition via either pathway, a new group of NER-related proteins is recruited to the site to take over the process of removing the damage. The researchers discovered that these proteins work together to separate the two strands of DNA, much like unzipping a zipper from the center, to create a space—"bubble"—where proteins can confirm the damaged strand of DNA and cut it out.

The findings from this study have revealed key roles for several proteins involved in the NER process for repairing DNA damage. The importance of these proteins in maintaining health is highlighted by cases where compromised protein function is associated with certain cancers and disorders. NER is also thought to contribute to resistance to some chemotherapy drugs. This study’s findings could enable the development of more effective cancer treatments and potential genetic therapies targeting the NER process.


BUILDING BETTER RESEARCH TOOLS

Improved RNA Detection Technique Enhances Ability to Monitor Cellular Messages: Scientists have improved an existing technique to detect RNA messages inside cells, making it faster and cheaper to simultaneously track the activity of multiple genes. Messenger RNAs (mRNAs) carry protein assembly instructions from genes to the cellular machinery where proteins are made. Technologies that track which mRNAs are in what cells at what time can be powerful, versatile tools. These tools can help researchers better understand the roles of the proteins the mRNAs encode, especially in processes where the activity of many genes changes at once, such as when healthy cells are disrupted by disease.

Researchers have now reported on improvements to one RNA detection method, called clampFISH. This technique uses a series of probes customized to stick to mRNAs encoding instructions for a specific protein of interest. A large molecular scaffold is then built over the mRNA, binding fluorescent dyes that amplify the
relatively weak “signal” from a single mRNA so it can be detected by microscopy. A weakness of the original “clampFISH 1.0” procedure, however, was that it was relatively expensive and time-consuming, especially when detecting multiple different mRNAs at once.

To create clampFISH 2.0, the scientists modified the structure of the scaffold and streamlined the protocol to make it faster and cheaper. They verified that clampFISH 2.0 still accurately and precisely detected targeted mRNAs and that it could pinpoint an mRNA’s location within a cell. ClampFISH 2.0 also generated a strong enough signal to allow imaging by lower-powered microscopes with wider fields of view, which allowed researchers to analyze cells faster. This feature was particularly useful in studying rare events. For example, scientists used clampFISH 2.0 in a very large tumor cell sample to measure the simultaneous activity of 10 genes, observing for the first time how those genes activate together in rare instances that can lead to drug resistance. Researchers also performed a similar analysis on preserved tumor tissue, such as would be generated by a cancer biopsy.

Overall, the streamlined clampFISH 2.0 procedure was shown to be a rapid and flexible tool to efficiently detect multiple mRNAs at once, allowing the study of research questions previously hindered by technical limitations.

Pathways to Health for All: A New Report From NIDDK’s Health Disparities and Health Equity Research Working Group of Council

In Spring 2023, NIDDK announced the release of Pathways to Health for All, a new report from the Health Disparities and Health Equity Research Working Group of the NIDDK Advisory Council. The Report makes innovative recommendations to advance research in health equity and health disparities. It also includes guiding principles for embedding equity into research and tips for researchers, both at NIDDK and externally, who plan to engage in robust health equity research.

Many of the diseases and conditions in NIDDK’s research mission disproportionately affect racial and ethnic minority populations and others who are medically underserved or marginalized. Health equity means that people of all backgrounds and ages have fair and just opportunities to live long, healthy, productive lives. The social and structural drivers of health disparities operate in multiple sectors and at levels beyond NIDDK’s traditional scope, but research can make a valuable contribution toward advancing health equity. Importantly, social determinants of health—the conditions in which people are born, grow, work, live, and age—can be primary contributors to health inequities among groups that are socially or economically marginalized.

The report presents five overarching research recommendations, each with corresponding opportunities, for high-impact research and actionable strategies:

1. Strengthen community engagement through partnership, power sharing, and capacity building to improve research

2. Advance research on the mechanisms by which biological, behavioral, environmental, and structural factors interact to affect health, disease, and resilience
3. Advance research on interventions and studies to address racism, health-related social needs, and social determinants of health

4. Promote new methods, measures, tools, and technologies to accelerate achievement of health equity research goals

5. Enhance NIDDK collaboration, structures, and programs to support robust research in health equity

Community members—including patients, caregivers, and others living with or at risk for diseases within NIDDK’s mission—were involved throughout the report development process as Working Group members who shared their lived experiences, perspectives, values, and priorities. These insights are featured in call-out boxes throughout the report. One member commented, “It made me proud and honored that my opinion was valued, and it made me want to go out and do research in the community to see what is missing or where we can help or fill the void to respond to the community’s voice or the community’s calling.” Another remarked, “I believe participating in this group will facilitate change for us that feel we have been left behind.”

NIDDK thanks the Working Group participants, including Council members, community members, patients, caregivers, NIDDK staff, and external researchers across the country, who contributed their time, expertise, and perspectives to this project. NIDDK research can foster scientific breakthroughs, provide the evidence base needed for equitable and effective clinical practice, and inform public health programs and policies. NIDDK is poised to act—both within its traditional scope and with innovative strategies and collaborations—to implement the recommendations in the report to effect meaningful change within its research mission.
Mentorship and the NIDDK Commitment to Increasing Scientific Workforce Diversity

Strengthening biomedical research workforce diversity and training is a cross-cutting theme in the NIDDK Strategic Plan for Research, and the importance of nurturing a diverse, world-class workforce is one of the core values described in NIDDK’s report Pathways to Health for All. This is because research shows that diverse teams working together and capitalizing on innovative ideas and distinct perspectives outperform homogenous teams. Scientists and trainees from diverse backgrounds and life experiences bring different perspectives, creativity, and individual interests to address complex problems. In this way, they foster scientific innovation, enhance global competitiveness, contribute to robust learning environments, improve the quality of research, enhance public trust, and increase the likelihood that health disparities and the needs of underserved populations are addressed in biomedical research.

Studies also show that robust mentorship is an important predictor of success for researchers, including the ability to obtain research funding. Indeed, effective mentoring is critical for career advancement in biomedical research, particularly at early career stages and for individuals from underrepresented backgrounds. A National Academy of Sciences, Engineering, and Medicine report on the science of effective mentorship in science, technology, engineering, mathematics, and medicine highlights mentorship as a catalytic factor in an individual’s participation, persistence, and success in these fields. They also found that although mentorship has a particularly positive effect on individuals from underrepresented backgrounds, these individuals were also less likely to receive mentoring than were trainees from well-represented groups.

For these reasons, NIDDK has a long-standing commitment to fostering training and mentorship for diverse students interested in research careers and is continuously testing new approaches and maintaining existing programs, such as the Institute’s flagship partnership with the Network of Minority Health Research Investigators (NMRI). NMRI has had support from NIDDK through its Office of Minority Health Research Coordination for more than 20 years, but is “owned” by its members. NMRI’s success begins with the dedication of senior investigators to mentor and serve as role models for junior investigators and continues with their ongoing participation and with recruitment of new members.

Testimonials of those members are evidence for the power of this approach. For example, Deidra Crews, M.D., a professor in the Division of Nephrology at the Johns Hopkins University School of Medicine said, “NMRI has provided me with a network of colleagues across the country who are dedicated to improving the health of socially marginalized communities and has served as a collective source of mentorship and sponsorship throughout my career.” Likewise, Susan Brown, Ph.D., an associate professor in the University of California Davis Department of Internal Medicine calls NMRI “a gem. This community of generous and accomplished scholars offers a new entry intellectual home, where you can bring your whole self. NMRI offers a sense of connection and purpose that helped sustain me through the critical early years of my research career. This has been equally true during challenging times of professional transition, pandemic, and national social upheaval. It’s an honor and a privilege to continue as a member.”
Lina Huerta-Saenz, M.D., an assistant professor in the Department of Pediatrics, Division of Endocrinology at the Pennsylvania State University, recalls “a time during my career training in the United States when nobody looked like me in a room, and it was very hard to visualize myself in a future leadership position…. Now, I can see myself as a future leader because I know it is possible.” This transformation of outlook demonstrates why NMRI and other NIDDK scientific workforce diversity programs remain so important: as NIDDK Director Dr. Griffin Rodgers has noted, scientific ability is broadly distributed around the country and the world, but opportunity to build a successful scientific career is not.

Accordingly, NMRI is just one of the many approaches that NIDDK takes to advance scientific workforce diversity and mentorship. Others include the Diversity Supplement Program, which covers 2 years of costs, materials, and salaries for young researchers from backgrounds underrepresented in the biomedical workforce, and providing travel awards to attend the annual conferences of the National Medical Association and the National Hispanic Medical Association.

These efforts are complemented by diversity efforts supported by the extramural and intramural NIDDK Divisions. Recently, the Institute expanded such efforts with Helping to Accelerate Research Potential, a program designed to provide opportunities and mentorship for current NIDDK grantees, especially postdoctoral scholars and junior faculty from diverse backgrounds, to enhance their skills in areas that are critical for establishing and maintaining successful independent academic research careers. In addition, NIDDK Investigator Awards to Support Mentoring of Early Career Researchers from Diverse Backgrounds is an initiative designed to provide high-quality mentoring to graduate students and postdoctoral fellows from diverse backgrounds, including those from underrepresented groups, by established, NIDDK-funded scientists.

Together, each of these programs is helping to advance NIDDK’s research mission by developing a scientific workforce that realizes the tremendous, untapped potential of future scholars from every background and region of the Nation.