NIDDK

Recent Advances & Emerging Opportunities

Cross-Cutting Science

January 2022

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*

U.S. Department of Health and Human Services
National Institutes of Health
National Institute of Diabetes & Digestive & Kidney Diseases

NIH National Institute of Diabetes and Digestive and Kidney Diseases

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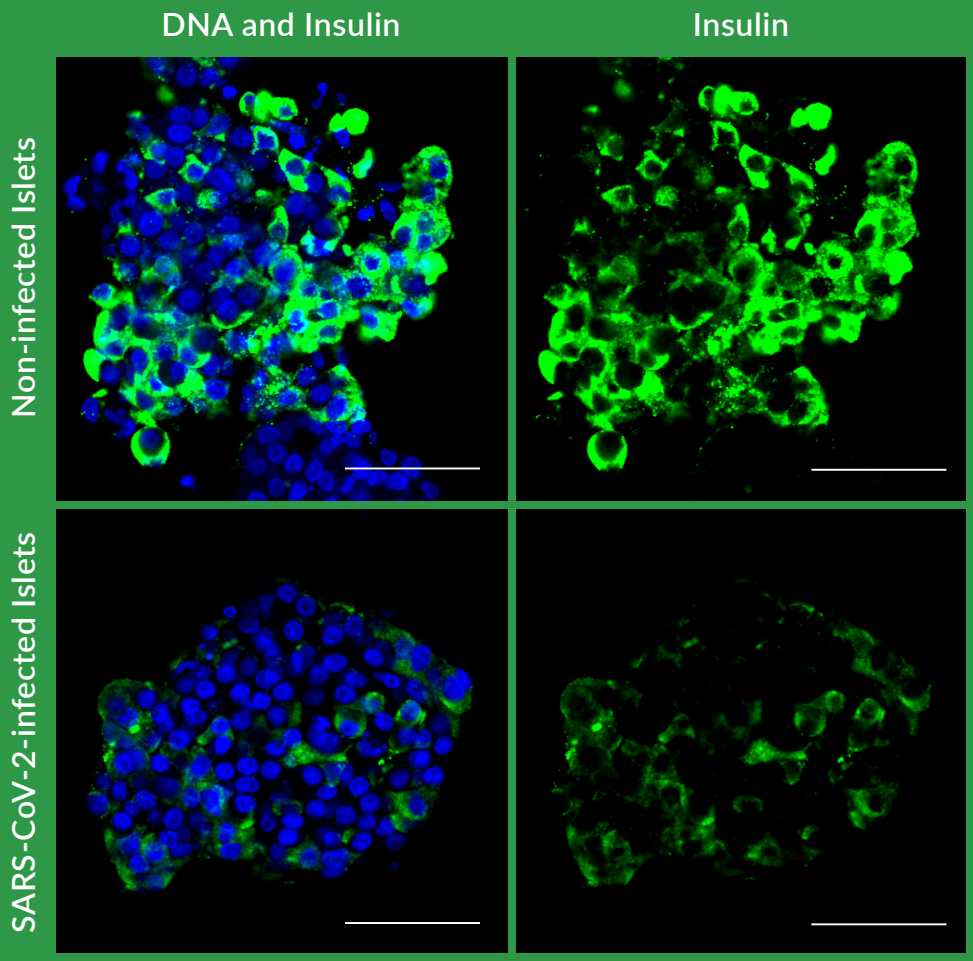

Previous research has shown that SARS-CoV-2 (the virus that causes COVID-19) uses its spike protein to anchor to another protein called ACE2 on the surface of human cells before infecting them. As described in this chapter, researchers have not only demonstrated SARS-CoV-2's ability to infect human pancreatic and liver cells but have also performed studies that are elucidating the impact of infection on diseases such as diabetes that are associated with greater health problems in people with COVID-19 and also may even be newly triggered or worsened by infection. For example, as shown in the images above, researchers found that the level of insulin (green) production detectable in beta cells of human pancreatic islets is much lower in islets newly infected with SARS-CoV-2 in the laboratory (bottom row) than in non-infected islets (top row). Combined with other findings, this significant change provides important insights into how COVID-19 can change the fate and function of cells important to the development and course of diabetes.

Panel images provided by Dr. Shuibing Chen, Weill Cornell Medicine. Originally published in Tang X, Uhl S, Zhang T,...Chen S. SARS-CoV-2 infection induces beta cell transdifferentiation. Cell Metab 33: 1577-1591, 2021. DOI: 10.1016/j.cmet.2021.05.015 and reprinted under the terms of the Creative Commons CC-BY license.

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 biologic 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.

There are also moments when the biomedical research enterprise is called upon to rapidly harness knowledge, resources, and expertise across many fields to meet extraordinary and urgent challenges that threaten the public health. The past year has seen triumphs in research to combat COVID-19, as effective, FDA-authorized vaccines developed by the NIH and others were quickly deployed across the Nation to protect people against the worst outcomes of infection. However, the battle with COVID-19 is not yet won, and research on treatments and on the pandemic's short- and long-term human health consequences continues.[1] At the same time, in the wake of sobering pandemic statistics and heart-wrenching events across the Nation, researchers have joined forces with diverse communities to find ways to identify, address, and ultimately overturn health disparities and promote health equity in the United States. Described in this chapter are examples of NIDDK efforts to overcome these critical challenges through research and scientific workforce development for the betterment of public health today and into the future.

COVID-19: A CONTINUING STORY

Since its recognition as a pandemic disease in early 2020, COVID-19 has brought illness, disability, and death to millions of people in the United States and around the world, while upending lives and normal activities for many millions more. People who contract the disease, which is caused by SARS-coronavirus-2, or SARS-CoV-2, can find themselves facing anything from a mild, cold-like illness to life-threatening symptoms that land them in a hospital intensive care unit. While the most obvious symptoms experienced by the majority of people with severe COVID-19 disease are respiratory, SARS-CoV-2 infection can cause damage to organs and tissues throughout the body.[2] Moreover, although people of any age or state of health can contract the virus, those with chronic diseases such as type 2 diabetes, obesity, chronic kidney disease, and chronic liver disease are at greater risk of developing severe disease leading to hospitalization and death.[3]

Critical findings about COVID-19 and its relationship to diseases such as diabetes and liver and kidney disease have already emerged from NIDDK-supported studies.

The NIH has pursued a multi-pronged approach to balance the enormous and acute research needs imposed by COVID-19 with the research it supports to benefit the health of people with or at risk of many other diseases and conditions. Thus, throughout the course of the pandemic, the NIDDK and other NIH Institutes and Centers have sought to mitigate its impact on biomedical research and the scientific workforce. These efforts have included new flexibilities in the receipt, review, and funding of research and researcher training grant applications, which have been made available to help

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[1] *See https://covid19.nih.gov/ for comprehensive information on the NIH research response to COVID-19, including efforts focused on vaccine development and testing, improved COVID-19 testing strategies, more effective treatments, reducing disparities, better basic understanding of the virus that causes COVID-19, and the lingering effects of the disease in many individuals (sometimes referred to as "long-COVID" or Post-Acute Sequelae of SARS-CoV-2).*

[2] *Gupta A, et al. Nat Med 26: 1017-1032, 2020.*

[3] *Centers for Disease Control and Prevention: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html. Accessed November 5, 2021.*

sustain investigators in the face of pandemic-induced disruptions to research and research career advancement. For example, for scientists at early career stages—who are particularly vulnerable to deleterious career impacts—the NIDDK provided opportunities to extend their existing research training and career development funding for up to 1 year, providing a little more breathing room so these individuals could apply for their next grants or search for the next jobs in their careers. The NIDDK has also worked with its clinical trial investigators to ensure participant safety and research progress as studies reopened, and to launch several much-needed clinical trials and studies after delays imposed by COVID-19.

NIDDK Research and COVID-19

Understanding and preventing COVID-19's deleterious effects on people who have diseases and conditions within the NIDDK's mission are important goals for the Institute. Alarmingly, there is also evidence that COVID-19 can increase people's risk for developing acute or chronic diseases. Thus, in 2021 the NIDDK supported multiple research efforts to address these areas of concern. For example, the NIDDK organized a meeting of the Diabetes Mellitus Interagency Coordinating Committee (DMICC) in March so that leading diabetes researchers and DMICC representatives from across the federal government could review what data had emerged to date about diabetes and COVID-19. They identified numerous challenges to address in such areas as health disparities, the effects of diabetes treatments on COVID-19 outcomes, and the influence of each disease on the course of the other. As co-chair of the NIH Obesity Research Task Force, the NIDDK also hosted a virtual symposium on "Obesity and COVID-19" in September (*see feature in the Obesity chapter*).

There have also been opportunities for NIDDK-supported research projects and programs to pivot some activities toward COVID-19. For example, the NIDDK Diabetes Centers program has actively pursued efforts to leverage infrastructure, facilities, and internal programs to address COVID-19 and diabetes. Researchers have also been able to leverage their NIDDK-supported projects toward COVID-19 through supplemental support from central NIH COVID-19 initiatives—for example, the NIH Rapid Acceleration of Diagnostics initiative has provided supplemental funding to an NIDDK-supported diabetes center to scale rapidly a COVID-19 testing program for people in Georgia at high risk due to diabetes and other metabolic disease. NIDDK staff have also been active in helping to shape trans-NIH efforts that could help people with COVID-19 who are also affected by diseases within the NIDDK research mission both in the near term and in the future.

Importantly, critical findings about COVID-19 and its relationship to diseases such as diabetes and liver and kidney diseases, have already emerged from teams of intramural and extramural researchers supported in whole or in part by the NIDDK, some of which are summarized below. To continue this course of discovery, the NIDDK recently funded a variety of basic and clinical research projects focused on understanding mechanisms underlying the impact of COVID-19 on organs, tissues, and biological systems within the Institute's purview. These projects may also contribute to our understanding of the lingering symptoms experienced by many people who have had COVID-19.

Moving Forward in the Era of COVID-19

The NIDDK is encouraged by the enormous achievements we have seen in a short span of time. In particular, the rapid development of effective vaccines has been critical to saving lives and preserving health. However, the overall impact of the pandemic has been extremely sobering. As is the case with many infectious diseases, COVID-19 may be with us for a long time, testing our endurance, ingenuity, and health. There are challenges imposed by emerging viral variants, health disparities, and the continued need for interventions that can protect people for whom COVID-19 vaccines are not fully effective—just to name a few. As the Nation continues its battle to emerge from the pandemic, the NIDDK will continue seeking to ensure the health and safety of researchers, study volunteers, and patients, while also helping to maintain research progress and a robust scientific workforce across all the areas within its research mission.

In the era of COVID-19, the NIDDK continues to strive toward ensuring the health and safety of researchers, study volunteers, and patients, while maintaining research progress and a robust scientific workforce across all the areas within its research mission.

PROGRESS IN UNDERSTANDING MULTIPLE IMPACTS OF COVID-19 ON THE BODY

New Insights into Links Between SARS-CoV-2 Infection and Diabetes: Research has revealed that the virus causing COVID-19 can infect pancreatic β (beta) cells, changing their function—a critical discovery toward understanding a devastating relationship between COVID-19 and chronic disease. Despite SARS-CoV-2 being primarily a respiratory virus, it affects multiple organs and systems during acute illness and sets the stage for long-term symptoms in a significant proportion of those infected. Thus, understanding the mechanisms underlying COVID-19's many complications and comorbidities is important to reducing the tremendous burden this disease is already imposing on people and health care systems around the world. For example, people with diabetes are at higher risk for grave outcomes from COVID-19. Moreover, researchers are trying to figure out whether SARS-CoV-2 infection may also trigger new onset of diabetes, as there is increasing evidence with the number of new cases appearing after infection. One unanswered question is whether SARS-CoV-2 exerts such effects through direct infection of susceptible cells and tissues.

In an initial study, researchers demonstrated in laboratory models how SARS-CoV-2 infects certain human cells and tissues—including pancreatic β cells and liver cells. They also found that donated human pancreatic islets were susceptible to SARS-CoV-2 infection. The team then collaborated with additional researchers to investigate whether or not β-cell infection also occurred in people infected with SARS-CoV-2, and, if so, what effects this had on the cells. Comparisons of islets from deceased human donors showed molecular signatures of SARS-CoV-2 in the β cells of those who had died from COVID-19. Closer examination of islets infected with SARS-CoV-2 in the laboratory revealed that infected β cells produced less insulin and produced proteins normally made by other pancreatic cells—suggesting that infection was causing them to change their function, or "transdifferentiate." A similar pattern of changes was also seen in islets from deceased donors with COVID-19, confirming that SARS-CoV-2 infection can alter β-cell activity in people.

Further analysis suggested that an intracellular pathway activated in response to viral infection and other stressors was governing the observed β-cell changes. Using artificially transdifferentiated human cells, the scientists identified a chemical that in subsequent experiments blocked the β-cell transdifferentiation process upon SARS-CoV-2 infection, most likely through inhibition of virus-induced changes to the identified stress-activated pathway. These results not only suggest that SARS-CoV-2 infection directly induces changes in β cells that could affect the course or onset of diabetes, but also provide hope that this process may be preventable.

Tang X, Uhl S, Zhang T,...Chen S. SARS-CoV-2 infection induces beta cell transdifferentiation. Cell Metab 33: 1577-1591, 2021.

Yang L, Han Y, Nilsson-Payant BE,...Chen S. A human pluripotent stem cell-based platform to study SARS-CoV-2 tropism and model virus infection in human cells and organoids. Cell Stem Cell 27: 125–136, 2020.

Evidence for SARS-CoV-2 infection and reprogramming of β cells provides new insights into the multi-faceted impact of this virus.

COVID-19 and Liver Injury: Researchers have identified a link between an immune system factor and promotion of blood vessel damage that may explain liver injury in people with COVID-19—and help to inform future research efforts to prevent and combat such liver damage. People with COVID-19 commonly have liver injury. This injury appears to be linked to vascular (blood vessel) damage, but the underlying mechanisms have been elusive. A hint came from the observation that people with COVID-19 have elevated levels of an immune system factor called IL-6 in their blood, along with factors that either promote damage to cells lining blood vessels and/or enhance blood clot formation. This suggested that COVID-19-induced liver injury could be mediated through cells called liver sinusoidal endothelial cells, or LSECs, highly specialized cells that line the tiniest blood vessels in the liver and are critical to proper liver function and health. LSECs are both prime targets for damage and producers of factors involved

Liver injury is commonly seen in people hospitalized with COVID-19. A new study reveals a mechanism that could explain why and how this occurs, providing insights important to evaluating COVID-19 induced liver damage and finding ways to prevent and treat it.

in inflammation and clotting—production that could be stimulated by IL-6.

In support of this hypothesis, researchers found that among people hospitalized with COVID-19, higher levels of a liver injury biomarker correlated with higher levels of factors that promote blood clotting—including one produced primarily by LSECs, called factor VIII—as well as biomarkers of inflammation and IL-6. Comparing liver specimens from deceased donors at a microscopic level, the scientists found a similar pattern: among donors who had had COVID-19, those who had higher levels of the liver injury biomarker showed a greater abundance of cells and factors involved in injury, inflammation, and clotting in the vicinity of LSECs. This finding also tracked with higher levels of IL-6, again suggesting a role for this immune system factor. To test the possible role of IL-6 directly, the researchers treated laboratory samples of human LSECs with a complex of IL-6 and a soluble form of its receptor protein. They found that IL-6-treated LSECs produced several of the proinflammatory and clotting factors seen in people with COVID-19 and liver injury—a response that could be blocked by further treating the cells with inhibitors of this IL-6 signaling pathway.

Together with other experimental results, these study findings provide evidence that liver injury in COVID-19 may be mediated by IL-6 acting on LSECs, a mechanism that could be targeted therapeutically to prevent and effectively treat liver damage.

McConnnell MJ, Kawaguchi N, Kondo R,...Iwakiri Y. Liver injury in COVID-19 and IL-6 trans-signaling-induced endotheliopathy. J Hepatol 75: 647-658, 2021.

Blood-based Biomarker May Both Predict COVID-19 Severity and Explain Tissue Injury: Researchers have found that changes to the amounts and types of DNA present in the blood of people with COVID-19 not only correlate with disease severity but may also be mediating injury to kidneys and other organs—a discovery that could help tailor clinical management and advance treatment for COVID-19.

People normally have a small amount of DNA in their blood that isn't contained within cells. This so-called "cell-free DNA," or cfDNA, usually comes from the cells that give rise to immune system and blood cells. However, the source, amount, and characteristics of cfDNA can change in certain diseases and conditions—sometimes before symptoms are apparent—so cfDNA

Researchers have identified a potential blood-based biomarker for COVID-19 disease severity and tissue injury that could aid efforts to improve disease outcomes for people.

can be a useful tool in diagnosing and treating disease. Because COVID-19 severity varies so much from person to person, researchers wondered whether cfDNA could be an easy and useful way to predict COVID-19 outcomes. To find out, they evaluated blood samples voluntarily provided by 85 people with COVID-19 across the spectrum of disease severity, from non-hospitalized people with mild symptoms to hospitalized people requiring intensive care. They also evaluated blood samples from people without COVID-19 for comparison. The results showed that the people with COVID-19 not only had markedly higher levels of cfDNA overall early in the course of disease, but also that higher amounts of certain types of cfDNA correlated with more severe disease and even death. Moreover, the researchers found that multiple tissues and organs contributed to the elevated cfDNA, including lung, blood vessels, liver, heart, fat tissue, and kidney, and that in some cases tissue-specific cfDNA correlated with known markers of inflammation and tissue injury.

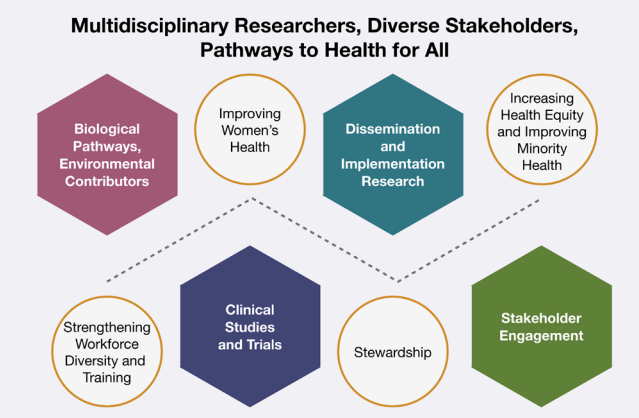
Based upon other research, the team also suspected that elevated cfDNA might not just be a marker of COVID-19 disease severity and tissue injury but also might incite some of that injury itself. Through experiments using laboratory grown mouse kidney cells, they found that exposure to the cfDNA from people with COVID-19 caused the cells to overproduce a potentially self-damaging molecule—a process that could largely be prevented by adding an inhibitor of the pathway thought to mediate this kidney cell response to cfDNA. Together, these findings—made possible by generous patient volunteers, some of whom did not survive COVID-19—not only suggest that cfDNA could be useful for predicting disease severity, but might also point the way to treatments that stave off some COVID-19-induced tissue injury.

Andargie TE, Tsuji N, Seifuddin F, ... Agbor-Enoh S. Cell-free DNA maps COVID-19 tissue injury and risk of death and can cause tissue injury. JCI Insight 6: e147610, 2021.

The NIDDK Strategic Plan for Research: Pathways to Health for All

In December 2021, the NIDDK released the Strategic Plan for Research, which presents a broad vision for accelerating research over the next 5 years to improve the health of people who have or are at risk for diseases within our mission. This overarching Strategic Plan complements the NIDDK's disease-specific planning efforts and will guide the Institute to build on its over 70 years of discovery, progress, and innovation.

The Strategic Plan is based on extensive input from leading researchers and patient advocates across the country who served on a strategic plan working group, numerous organizations and individuals who provided ideas in response to public Requests for Information, and members of the NIDDK's Advisory Council. It includes four major Scientific Goals, each with a set of research opportunities, around a unifying theme: to empower a multidisciplinary research community, engage diverse stakeholders, and leverage discoveries of connections among diseases to improve prevention, treatment, and health equity—pathways to health for all. Woven throughout the Plan are cross-cutting topics that are integral to all the Scientific Goals: reducing health disparities and increasing health equity among racial and ethnic minority populations and others who are underserved; improving women's health; strengthening biomedical workforce diversity and training; and serving as an efficient and effective steward of public resources.



This image depicts the key components of the Strategic Plan, including four major Scientific Goals (shown in hexagons) and cross-cutting topics crucial to the NIDDK's mission (shown in circles).

> *To improve the health of people who have or are at risk for diseases in the NIDDK mission, the Institute is committed to empowering a multidisciplinary research community; engaging diverse stakeholders; and leveraging discoveries of connections among diseases to improve prevention, treatment, and health equity—pursuing pathways to health for all. This unifying theme is highlighted throughout the Strategic Plan.*

The Strategic Plan's four major Scientific Goals are to:

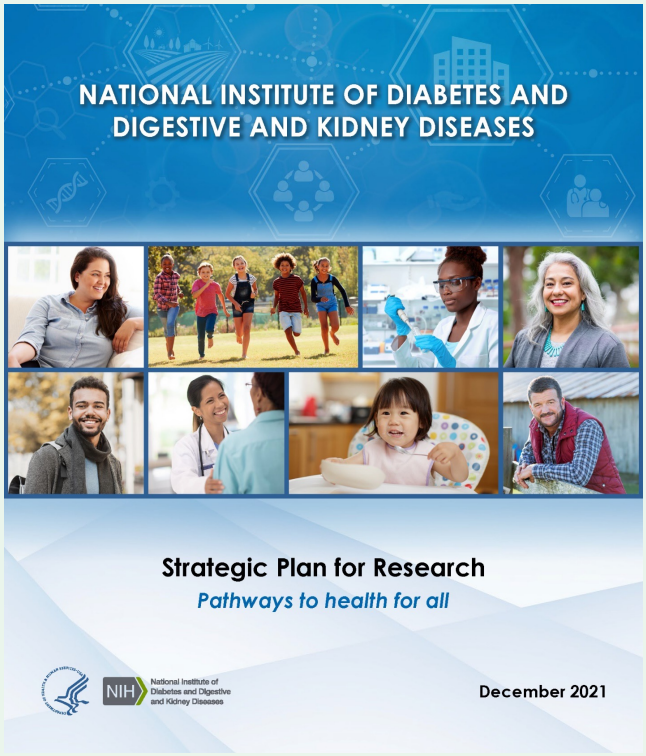
1. Advance understanding of biological pathways and environmental contributors to health and disease;

2. Advance pivotal clinical studies and trials for prevention, treatment, and cures in diverse populations;

3. Advance research to disseminate and implement evidence-based prevention strategies and treatments in clinics and community settings, to improve the health of all people, more rapidly and more effectively; and

4. Advance stakeholder engagement, including patients and other participants as true partners in research.

For each Scientific Goal, the Strategic Plan presents known challenges, recent advances and discoveries to build on, and a set of broad research opportunities. The Plan also highlights the NIDDK's commitment to serve as an efficient and effective steward of public resources. The



Institute will monitor the progress toward each Scientific Goal and identify areas to strengthen efforts, build on discoveries, and pursue emerging research opportunities. Progress will be shared with stakeholders in future editions of this publication and other venues. (Further information about the goals, research opportunities, stewardship, and the planning process is in the Strategic Plan, available on the NIDDK's website.)

The NIDDK is grateful to all who contributed to the Plan's development, and looks forward to working with communities who share the NIDDK's interest in research to improve people's health and quality of life.

NIDDK Efforts To Promote Scientific Workforce Diversity

While NIDDK researchers from every race and ethnicity are striving to help achieve health equity, the Institute believes that these vital efforts would be strengthened by having a scientific workforce that better reflects the diverse backgrounds and experiences of the U.S. population. While scientific talent is surely well represented across all groups, opportunity is not. The NIDDK is therefore committed to overcoming the dearth of minority scientists across its mission areas. The NIDDK's Office of Minority Health Research Coordination (OMHRC) works with the NIDDK extramural and intramural research divisions to lead these efforts.

One example of these efforts includes a collaboration, which began in 2003, between the NIDDK and the National Center for Research Resources to support the development and implementation of curriculum-based programs to train diverse doctoral and post-doctoral candidates in clinical research. In 2006, the collaboration ended, but the NIDDK continued the effort through several iterations, culminating in the current program, the Small Grants for New Investigators To Promote Diversity in Health-related Research, in collaboration with the National Human Genome Research Institute. From fiscal years 2010 through 2020, the program provided more than 60 such grants to mostly early career investigators from underrepresented minority groups, several of whom went on to compete successfully for traditional NIH research grants.

The NIDDK also provides support for diverse young investigators through partnerships with professional societies, which are uniquely positioned to work toward enhancing diversity in the biomedical research workforce. These organizations sponsor awards for promising young investigators and have a history of supporting the career development of their members—mechanisms they can harness to diversify the biomedical research workforce. Accordingly, the OMHRC created the Partnerships with Professional Societies to Enhance Scientific Workforce Diversity and Promote Scientific Leadership Program. This initiative supports grants to societies with a focus on NIDDK mission areas to establish or expand training and career development programs for junior investigators from underrepresented backgrounds.

For example, one such grant enabled the American Gastroenterological Association (AGA) to establish a program called Fostering Opportunities Resulting in Workforce and Research Diversity (FORWARD) that supports underrepresented physician scientists to develop leadership skills, strengthen their research and management skills, and receive mentorship and training from top gastrointestinal investigators. FORWARD scholars participate in the AGA Leadership Development Conference, attend trainings for writing grant proposals and scientific manuscripts, and attend an academic skills workshop. Similarly, a grant to the Endocrine Society supports its Future Leaders Advancing Research in Endocrinology (FLARE) program for basic and clinical research trainees and junior faculty from underrepresented communities who have demonstrated achievement in endocrine research. The program provides structured leadership development and in-depth and practical training in topics ranging from grant writing to lab management. FLARE participants attend an annual workshop where they can network and develop skills such as: identifying and applying for funding, time and lab management, communication, and career development.

These initiatives reinforce other OMHRC programs that support research training for underrepresented minority students in high school and college and are part of the NIDDK's efforts to bring more and more talented individuals from an array of backgrounds into research.

For example, the STEP-UP program provides high school and undergraduate students with biomedical research opportunities for the summer. At the graduate school level, the NIDDK provides scholarship support to students from underrepresented and underserved communities to complete their Ph.D. or M.D./Ph.D. degrees. For

individuals at various stages of their research careers post-doctoral and higher, the NIDDK established the Network of Minority Health Research Investigators to provide mentoring and other information and support for scientists from underrepresented groups and others interested in minority health. The NIDDK's Diversity Supplement Program provides support for promising researchers from backgrounds underrepresented in biomedical research as they gather preliminary data to apply for their own independent research awards.

The NIDDK firmly believes that the overall biomedical research enterprise will be greatly strengthened by the scientific ideas and talent of people currently underrepresented in research and will help lead us toward health equity for all Americans.