The NIDDK Information Network—dkNET—was launched in 2014 to promote sharing of information within and among NIDDK’s research communities. dkNET’s goal is to ensure that data and resources generated from NIDDK-supported research can easily be found, used, and re-used to answer future scientific questions. dkNET accomplishes this by being a search engine for many data repositories and for sources of cells, mouse models, and other research tools. For more information about dkNET, see the feature in this chapter.
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 the fundamental biologic building blocks and processes of an organism—its 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 knowledge of disease and disease treatment can be traced to laboratory studies whose relevance to health could not have been fully known or appreciated at the time they were conducted.

With the development of innovative scientific technologies and the emergence of new scientific disciplines as talented and creative research teams join together to tackle ever more complex challenges, new opportunities to make exciting discoveries arise each day. The insights gained through this research can be expected to further scientific progress in many research areas, for today’s discoveries may hold the seeds of tomorrow’s cures.

This chapter provides a few examples of the Institute’s commitment to basic and applied research relevant across a broad spectrum of scientific disciplines. For example, features in this chapter highlight: the research of NIDDK-funded investigators who have won the distinguished Presidential Early Career Award for Scientists and Engineers; a workshop on the emerging role of branched chain amino acids in human diseases; and an exciting set of research resources available to the scientific community through the NIDDK Information Network (dkNET).

FIRST STRUCTURE OF AN IMPORTANT CLASS OF MEMBRANE PROTEINS

Painting a Portrait of a Trio of Proteins Important in Health: A G-protein-coupled Receptor and Its Molecular Partners: Using a cutting-edge technique, researchers have determined the structure of a protein that helps control blood glucose (sugar) levels, the GLP-1 receptor (GLP1R). When GLP-1 hormone binds to it, the GLP1R interacts with another protein partner that helps carry the hormone’s message within the cell. This receptor is part of a family of proteins, called class B G-protein coupled receptors (BGPCRs), that have key roles in many critical physiologic processes, including regulating levels of calcium in the blood and maintaining the balance of water and electrolytes in the body. Each member of this protein family spans cellular membranes in the tissues where they function. In general, it is known that when the part of a BGPCR that lies outside the cell binds to its particular hormone, changes occur in the receptor’s structure within the cell membrane that promote binding to and activation of a second protein, called a G protein. The G protein then carries the signal into the cell and triggers the appropriate response to the hormone. Given their important roles in human health, understanding the details of BGPCR interactions with hormones and G proteins might aid in development of therapeutics that stimulate or inhibit individual BGPCRs, potentially improving treatment for multiple human diseases. Indeed, some medicines for type 2 diabetes act by stimulating GLP1R, which helps promote production of insulin in response to elevations of blood glucose (sugar) that occur after a meal, while slowing stomach emptying. Unfortunately, determining the structure of BGPCRs in complex with their hormones and G proteins has proved difficult using traditional techniques. In the hope of one day improving such medications and providing insights that could promote development of medicines that act on other GPCRs, scientists turned to a cutting-edge method called cryo-electron microscopy to determine the structure of GLP1R in complex both with the hormone GLP-1 and with a partner G protein.
In this approach, the researchers flash-froze membranes containing large numbers of GLP-1 receptors in complex both with the GLP-1 hormone and the receptor’s G protein partner. The very rapid drop to an extremely low temperature maintains the three-dimensional structure of the proteins and their relationship to one another and to the membrane, while avoiding the accumulation of ice crystals that might otherwise distort this arrangement. Next, they took transmission electron micrographs of the resulting samples. In this technique, a beam of electrons is passed through the sample. The frozen proteins interact with some of the electrons in the beam, and a receiver reconstructs an image of the sample based on these interactions. The resulting images of each individual GLP1R protein complex in the sample were somewhat fuzzy and indistinct; but by “averaging” the results from the many GLP1Rs in the sample using sophisticated software, the researchers were able to determine the structure of the receptor with remarkable precision. The adjacent figure shows two views of the GLP1R structure, where colors have been added to highlight specific parts of the protein, as well as GLP-1 and the G protein partner. (See the figure legend for details.) The researchers were able to use the resulting images to glean new information about how the proteins in the complex fit together, how the protein complex is predicted to move and bend as it carries out its function, and what these findings could teach about the structure and function of other GPCRs. This “portrait” is a remarkable technical achievement, and may one day advance health through improved understanding of the biology of GPCRs.


**EFFECTS OF THE BRAIN ON AGING**

**Cellular Understanding of How the Brain Controls Aging:** Researchers have discovered cellular mechanisms by which the brain regulates aging in mice, providing novel therapeutic targets to combat health consequences associated with aging. The research focused on cells, called adult neural stem/progenitor cells (NSCs), which through a complex signaling cascade called neurogenesis turn into mature nerve cells. NSCs are found in the hypothalamus, a part of the brain governing many physiologic functions, and in other brain regions, most notably, the hippocampus, involved in the formation of new memories and the site of early age-related degeneration in Alzheimer’s disease and related dementia (ADRD). The study examined whether NSCs in the hypothalamus were involved in regulating aging in male mice. First, the scientists observed that the number of NSCs declined with aging in mice. NSCs were abundant in the hypothalamus of young mice, diminished in middle-age mice, and were nearly entirely lost in aged animals. To determine if the loss of NSCs was causing the mice to age or was a consequence of aging, the scientists experimentally depleted most of the NSCs in the animals’ hypothalamis. Compared to control animals, mice lacking NSCs showed accelerating signs of aging, such as a shortened lifespan. These findings suggest that NSCs control the speed of aging.
Confirming this role, aging was slowed when NSCs were implanted into middle-age mice, with the animals living longer than their control counterparts. Because NSC loss or implantation produced effects on aging in a relatively short timeframe, the scientists hypothesized that the outcomes might be mediated by factors produced by the NSCs rather than by their maturation. Indeed, additional experiments showed that NSCs exert some of their anti-aging effects by secreting small particles called exosomes that contain microRNAs (miRNAs) into the cerebrospinal fluid of mice. miRNAs are involved in regulating gene activity and can be taken up by other cells. Thus, it appears that it is a specialized function of NSCs related to secreting these particles, rather than their function of turning into new mature nerve cells, that plays a key role in how NSCs govern aging in mice.

If NSCs play a similar role in women and men, they represent novel therapeutic targets to combat the health consequences associated with aging, such as diabetes and ADRD. Further research that delves into the detailed mechanisms by which these cells exert their effects—such as identifying what miRNAs are released by NSCs—may illuminate other targets and potential therapies.

dkNET: The NIDDK Information Network

Developing innovative strategies to enhance the sharing of data and resources remains an important focus for NIDDK. One of these strategies to enhance the ability to find, search, and reuse the science NIDDK supports is dkNET, the NIDDK Information Network.

Data science advances also continue to provide increasingly powerful and sophisticated technologies for integration and mining of data, offering new opportunities to use existing data to answer new questions. As biomedical tools and technologies improve, researchers are producing a rapidly increasing amount of data, tools, and resources. Organizing this information so that it can be easily found, searched, and reused is a continuing challenge. Resources and data from different studies can be stored in different public or private repositories, on different computer platforms, and in different formats. As a result, it can be extremely challenging for a researcher to locate resources relevant to their work, or to integrate data from different repositories in a useful way.

dkNET started in 2014 to promote sharing of information within and among NIDDK’s research communities. Its goal was to ensure that NIDDK-supported data and resources can easily be found, used, and reused to answer future scientific questions. dkNET accomplishes this by being a search engine for multiple data repositories along with sources of cells, mouse models, and other research tools.

dkNET has captured and indexed a wide variety of resources, including protocols and assays, antibodies, cell lines, animal models, data sets, and funding opportunities. dkNET’s resource catalogs are accessible via a user-friendly web portal, allowing users to search through millions of database records stored in hundreds of databases. dkNET also provides tools to enhance search efficiency; to create individualized workflows; and to analyze, visualize, and reuse data.

Currently, dkNET includes resources from sites such as AddGene, the Antibody Registry, the Beta Cell Biology Consortium, the Diabetic Complications Consortium, Grants.gov, the Nuclear Receptor Signaling Atlas, and various research animal repositories. dkNET continues to extend its reach by adding additional NIH programs and resource centers to its search function.

dkNET also supports the NIH’s Policy on Rigor and Reproducibility, which was released in 2015. dkNET was instrumental in supporting the development of Research Resource Identifiers, or RRIDs, which are unique authentication tags for biological resources such as mouse models and antibodies. Using RRIDs in their research allows scientists to specifically identify and track the reagents and resources used in a way that is not possible when using brand names, catalog numbers, or other identifiers that can change over time. dkNET provides services to help the scientific community easily find, use, and obtain RRIDs, which helps enhance transparency and reproducibility.

Resources like dkNET help ensure that scientists can build upon the work of the past to address “Big Science” questions now and in the future. As scientists continue to profile human biology in extraordinary depth, the ability to integrate, analyze, and search existing data sets will provide new opportunities to accelerate and transform biomedical research.
Two scientists supported by the NIDDK were among the recipients of the Presidential Early Career Award for Scientists and Engineers (PECASE) in 2017. The PECASE is awarded annually to scientists and engineers who, while early in their research careers, have pursued innovative research and shown outstanding scientific leadership. The two NIDDK extramural grantees who received the PECASE are Anna Greka, M.D., Ph.D., and Benjamin F. Voight, Ph.D.

Dr. Greka, an Assistant Professor at Harvard Medical School, received a PECASE award in recognition of her research investigating the roles of calcium ion channels in inherited kidney diseases. Her studies on the ion channel Transient Receptor Potential Channel 5 (TRPC5) revealed that blocking its activity with an inhibitor can protect mice from damage to the kidney’s filtration system, a finding that could lead to a new strategy to treat kidney disease.

Dr. Voight, an Associate Professor of Genetics at the University of Pennsylvania, received a PECASE award for his work using statistical and computational informatics to identify genetic variants that contribute to the risk of type 2 diabetes. Determining these variants could lead to improved understanding of the biology that contributes to type 2 diabetes, creating opportunities to develop novel therapeutics and prevention strategies and to personalize an individual’s risk.

In addition to the NIDDK-supported recipients, other scientists supported by NIH and other federal agencies also received the PECASE for their scientific achievements.

The PECASE is the most prestigious award given by the U.S. government to scientists at the outset of their independent research careers. These awards support the continued professional development of awardees, promote careers, foster innovation in science and technology, and recognize the scientific missions of participating agencies.

“These innovators are working to help keep the United States on the cutting edge, showing that Federal investments in science lead to advancements that expand our knowledge of the world around us and contribute to our economy.” - Barack Obama
What Are the Porphyrias?
The porphyrias are a group of metabolic disorders. The symptoms associated with porphyrias can be diverse and can be severe including chest and abdominal pain, emotional and mental disorders, seizures, and muscle weakness. These debilitating symptoms often appear quickly and can last for long periods of time. Environmental factors can trigger the symptoms of porphyria and include alcohol, smoking, certain drugs, hormones, stress, dieting and fasting, and exposure to sunlight. Avoiding sunlight has a major negative impact on quality of life, and the use of sunscreen is ineffective for porphyria symptoms.

The porphyrias mostly arise from an inherited mutation in any of eight genes that code for essential proteins in the heme production pathway—resulting in the accumulation of heme precursors and a blockage of heme production. Heme is a vital chemical compound that contains iron and gives blood its red color. It enables red blood cells to carry oxygen from the lungs to all parts of the body, and it also plays a role in the liver where it assists in breaking down chemicals including some drugs and hormones.

Diagnosis and Treatment
Diagnosis is difficult because the range of symptoms is common to many disorders, and interpretation of the tests may be complex. Although a large number of tests are available, the results among clinical laboratories are not always reliable. Treatments need to be improved and specific therapies developed.

Recent Findings from the Consortium
Inherent challenges to the development of rare disease treatments include difficulties in diagnosis, geographically dispersed patients and scientific experts, and lack of data on health of a group of people with a specific medical condition over time. The Consortium has begun to make inroads to overcome these challenges. For example, researchers have reported that different clinical laboratories have variability in measurement of erythrocyte (red blood cell) protoporphyrin, a biological molecule that is made during the production of heme. Because some of the measurement tests may lead to missed diagnoses, this finding identifies an area for improving diagnostic tests. Another study by the Consortium showed that higher levels of erythrocyte protoporphyrin were associated with increased disease severity and risk of liver dysfunction in people with forms of porphyria called erythropoietic protoporphyria or X-linked protoporphyria. The Consortium has also issued recommendations for the diagnosis, treatment, and counseling of patients with acute hepatic porphyrias.
The branched-chain amino acids (BCCAs), including leucine, isoleucine, and valine, are among the most highly represented amino acids in dietary protein. Based on a wealth of studies, they have emerged as more than simply essential components of our diet. Leucine in particular appears to be a key nutrient signal of a protein-containing meal and to play an important role in regulating metabolism and satiety signals. For example, leucine promotes release of the hormones GLP-1, insulin, and leptin, but inhibits the release of the hormone ghrelin. BCAAs and insulin are signals that promote energy storage and alter the growth of energy-consuming tissues. Intravenous infusion of BCAAs or consumption of dietary protein increase diet-induced thermogenesis (production of body heat) and energy wasting, more so than is associated with other nutrients, and may therefore help promote weight loss.

In May of 2017, the NIDDK held a conference, in cooperation with the NIH Office of Dietary Supplements and the Eunice Kennedy Shriver National Institute of Child Health and Human Development, to clarify whether these various actions of BCAAs are beneficial or detrimental to human health. This question is not straightforward, unfortunately, because scientific research exists in support of either conclusion.

For example, BCAA supplementation or BCAA-rich diets are often associated with improved body weight regulation, satiety, lean body mass, diet-induced thermogenesis, and muscle protein synthesis. Supplementation with BCAAs seems to result in health benefits in certain liver diseases, and has been investigated as a possible means to combat age-related loss of muscle mass.

On the other hand, there are reports of potentially adverse effects associated with BCAAs, particularly when present at high levels. For example, circulating levels of BCAAs are consistently increased in people with type 2 diabetes, insulin resistance, or obesity, where they positively correlate with insulin resistance and high levels of hemoglobin A1c, a marker of consistently elevated blood glucose (sugar). Several longitudinal studies have also reported that increased blood levels of BCAAs are predictive of future insulin resistance or type 2 diabetes, leading to speculation about a potential causative role for BCAAs. Abnormalities in BCAA metabolism leading to elevated levels are associated with various health problems. Some can lead to heart failure, while others underlie the pathology of Maple Syrup Urine Disease and a number of other rare genetic diseases. Additionally, a signaling system that has been implicated in cancer is activated by BCAAs. Another issue is that when circulating levels of BCAAs increase, they compete with the uptake of amino acid precursors of neurotransmitters in the brain, which can contribute to an increased risk of depression in individuals with obesity.

The NIDDK is the lead Institute at the NIH supporting studies of metabolism, nutrient signaling, obesity, type 2 diabetes, liver disease, and nutrition—all areas in which BCAAs appear to play an important role. Through this symposium, the NIDDK encouraged further research in this area, brought together the community studying BCAA signaling and metabolism with those interested in studying their role in health and disease, and sought to identify new research opportunities for understanding disorders affected by BCAAs.