The health benefits of exercise are well documented, but it is not understood what molecular changes are induced by physical activity or how these changes improve the function of different tissues and organs in the body to promote health. As described in this chapter, the Molecular Transducers of Physical Activity Consortium is a trans-NIH effort to build an extensive catalogue of biological molecules affected by exercise in people, construct a comprehensive molecular map of these changes, and characterize the functions of these key molecules. By doing so, researchers hope to link the exercise-induced molecular changes to the advantageous effects of physical activity. By determining how physical activity improves health and prevents disease at a molecular level, scientists can discover new therapeutic targets and develop new approaches to personalized exercise medicine.
Medical advances are not always achieved in great, intuitive leaps. More often, new prevention strategies, treatments, and cures result from a long, gradual accumulation of new 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 PECASE early career award, an NIDDK workshop on gastrointestinal and urologic care simulation technology, and a trans-NIH program, co-led by the NIDDK, to determine what molecular factors mediate the benefits of exercise. Another feature describes the NIDDK’s efforts to harness precision medicine to advance human health and develop more personalized therapies for diseases within the NIDDK’s mission.

**UNDERSTANDING MITOCHONDRIA’S RESPONSE TO STRESS**

**Stressed to the Breaking Point—How a Cell’s Mitochondria Respond to Stress To Maintain Health:** Scientists identified a key process for how mitochondria, the cell’s energy generators, or powerhouses, handle metabolic stress. Mitochondria are referred to as the “powerhouses” of the cell because they take energy that is ingested in the form of sugars or fats and convert it to fuel for the cell. Unhealthy mitochondria have been implicated in many disorders and diseases, including diabetes.

Cells typically contain many mitochondria, in some cell types up to several thousand. Mitochondria are dynamic, which allows them to maintain appropriate shape, size, and number. They are continually joining with one another (fusion) or splitting into smaller units (fragmentation or fission) in response to changing conditions. Metabolic stress, for example, induces mitochondria to undergo fragmentation; however the links between stress and the fission machinery have been poorly understood.

In a new study, scientists investigated whether a central metabolic sensor—adenosine monophosphate activated protein kinase (AMPK)—plays a role in triggering mitochondrial fragmentation due to metabolic stress. They found that treating a human cell line originally from bone tissue with chemicals that stress the mitochondria resulted in extensive fragmentation and activated AMPK. Genetically disrupting AMPK prevented fragmentation. Thus, the chemicals cannot trigger mitochondrial fission in cells that lack AMPK. To demonstrate further that AMPK provides a key signal for fragmentation, the researchers directly activated AMPK and found that this was sufficient to induce
mitochondrial fragmentation, even in the absence of the chemicals. They also activated AMPK in mouse cells with similar results, indicating that this function of AMPK is conserved.

Through additional experiments, the scientists found that AMPK triggers fission by activating a protein called MFF, which then recruits another protein (DRP1) to the membrane of mitochondria to induce fragmentation. They speculate that this process may be an important way for cells to rid themselves of damaged mitochondria. Additional research into the role that AMPK plays in regulating mitochondria may provide new insights into how mitochondrial stress affects metabolic diseases and disorders.


INSIGHTS INTO WOUND REPAIR

The Ties That Bind in Tissue Scaffold Assembly:
Scientists have defined an important role for chloride ions in the formation of the molecular scaffolding that provides structure and biological function in tissues throughout the body. Cells in many tissues are surrounded by a thin layer called a basement membrane (BM). These molecular scaffolds consist of proteins and chemicals that provide structural integrity and play a variety of functional roles in normal cellular biology and disease. For example, disruption of the collagen IV protein network in kidney BM can lead to a condition known as Alport’s syndrome, in which patients suffer from reduced kidney function and eventual kidney failure.

The assembly of collagen IV networks initially involves a two-step process. First, within cells, three individual, long, thin collagen protein chains wind around each other to form a triple-helical structure called a protomer, in which the tips on one end of each chain interact through a segment called an NC1 domain. Second, two separate protomers that are released from the cell bind together through these domains, forming an NC1 hexamer. Additional molecular steps then lead to the establishment of the collagen IV network in the BM.

To better understand how these complex collagen IV networks assemble, a team of scientists isolated the individual collagen protein chains and established conditions under which they spontaneously form protomers in the laboratory. The researchers tested different ions normally present in the BM and found that chloride ions were required for NC1 hexamer assembly; none of the other ions tested could promote these interactions at physiologically relevant concentrations. Using known information about the physical structure of NC1 domains, the scientists performed computer simulations to determine the effects of chloride ion interaction with specific amino acids (individual building blocks that link to form proteins) in the NC1 domains. The simulations predicted that binding of a chloride ion triggers changes in the shape of NC1 domains, thereby encouraging assembly. This prediction was confirmed when the researchers mutated these critical amino acids, which are largely conserved in collagen IV proteins across the animal kingdom, to prevent chloride binding, and the NC1 domains could no longer interact. They also examined the role of chloride in the BM of cells in culture, finding that chloride was required for collagen IV assembly under these more physiological conditions, not just in a test tube.

Together, these data uncover a role for chloride ions as signals that promote the assembly of collagen IV networks by inducing critical structural changes in NC1 domains that allow protomers to interact. This study could help provide a foundation of knowledge to develop strategies to prevent or treat diseases caused by dysfunctional BMs.

Dr. Gary Felsenfeld Receives Horwitz Prize: NIDDK Intramural Research Program Scientist Pioneered the Field of Epigenetics

Dr. Gary Felsenfeld, a senior investigator in NIDDK's Intramural Research Program and an NIH Distinguished Investigator, is a 2016 recipient of the Louisa Gross Horwitz Prize. Columbia University gives the award to recognize outstanding basic research in biology or biochemistry. Since the prize was first awarded in 1967, 43 awardees have gone on to win Nobel Prizes.

Dr. Felsenfeld's research has focused on how proteins that bind DNA in the cell's nucleus alter the structure and chemical nature of DNA. These interactions affect whether and when genes are "turned on or off," leading to the exquisite regulation of the cell's activities. Understanding the changes in these protein-DNA interactions that are associated with both normal and abnormal growth and development is essential to advancing progress in diseases such as diabetes and cancer.

Dr. Felsenfeld's pioneering work helped lead to the formation of this field of research, called "epigenetics." He has been a member of the NIDDK Intramural Research Program's Laboratory of Molecular Biology since 1961. In addition to his extraordinary research, Dr. Felsenfeld is an accomplished mentor, having trained numerous scientists who have gone on to distinguished research careers.

(Information adapted from original article by Krysten Carrera, published on September 23, 2016 in the NIH Record.)
Three scientists supported by the NIDDK have received the Presidential Early Career Award for Scientists and Engineers (PECASE) in 2016. 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. Among the recipients were three NIDDK extramural grantees—Camilla Forsberg, Ph.D., David J. Pagliarini, Ph.D., and Kay Maxine Tye, Ph.D.

Dr. Forsberg, a Professor of Biomedical Engineering at the University of California, Santa Cruz, received a PECASE award in recognition of her work to understand the mechanisms that regulate stem cell fate decisions. Her studies on hematopoietic stem cells (which give rise to all other blood cells) concentrated on finding new insights into how the blood and immune system is established and may guide strategies for combating blood disorders.

Dr. Pagliarini, an Associate Professor of Biochemistry at the University of Wisconsin-Madison and Director of the Metabolism Research Group at the Morgridge Institute for Research, received a PECASE award for his investigations into mitochondrial proteins and the development of disease. His research focuses on the types of mitochondrial dysfunction that can contribute to conditions such as type 2 diabetes and obesity.

Dr. Tye, an Assistant Professor at the Picower Institute for Learning and Memory in the Department of Brain and Cognitive Sciences at the Massachusetts Institute of Technology, received a PECASE award in honor of her studies to develop and apply new technologies to address compulsive sugar intake. Her research explores the brain activity involved in unhealthy eating choices and habits that can lead to obesity.

In addition to the NIDDK-supported recipients, 17 other scientists supported by the NIH received the PECASE for their scientific achievements. The NIH has funded 253 PECASE recipients since the award’s inception in 1996.

The PECASE is the most prestigious award given in the United States 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. A list of NIH scientists who have received this prestigious award is available at: [http://grants.nih.gov/grants/policy/pecase.htm](http://grants.nih.gov/grants/policy/pecase.htm)
Contrary to its name, a “one size fits all” clothing garment will not actually fit everyone. It may be a perfect fit for some, but it will be too big or too small on others. It is not made with each individual in mind.

The same could be said for most of today's medical treatments. Most treatments are also “one size fits all,” which may work well for some people but not for others. Just as clothing fits better when a tailor alters it to fit the individual, medical treatments could also work better if they were tailored to the person. That is the goal of precision medicine—to move away from a “one size fits all” approach so that health care decisions are personalized and based on individual variability in genes, environment, and lifestyle.

Precision medicine would take into account these differences between individuals and enable health care that predicts more accurately which treatment and prevention strategies will work in specific people.

Already, precision medicine has some applications across a number of diseases. To extend the benefits of precision medicine to more diseases, the NIH launched the All of Us Research Program® as a part of the Precision Medicine Initiative®. All of Us involves building a national research cohort of 1 million or more U.S. volunteers who broadly reflect the diversity of the country’s population; cohort recruitment started in 2016. Using information and biological samples provided by the cohort, researchers will begin teasing out how genetics, environment, lifestyle, and other factors contribute to an individual’s health and disease, including diseases and disorders within the NIDDK mission. More information about the All of Us Research Program is available at: www.nih.gov/research-training/allofus-research-program

Complementing the All of Us Research Program, the NIDDK also supports research toward precision medicine. For example, an ongoing clinical trial, called GRADE, is comparing the long-term benefits and risks of four widely used diabetes drugs in combination with metformin for treating people with type 2 diabetes. Results are expected to shed light on factors that are associated with response to and failure of the different treatments, which could promote personalized therapy.

Additionally, analysis of extensive genetics data from the Inflammatory Bowel Disease (IBD) Genetics Consortium contributed to a more precise classification of the different types of IBD. Knowing what type of IBD a person has could eventually help health care providers offer personalized treatments. A new Kidney Precision Medicine Project aims to build on recent observations that chronic kidney disease (CKD) and acute kidney injury (AKI) are not single, uniform diseases. Defining subgroups of CKD and AKI—and understanding underlying molecular pathways—can facilitate identification of specific drug targets and enable individualized care.

Knowledge stemming from these and other NIDDK- and NIH-supported research efforts can move health care away from a current “one size fits all” approach for most medical treatments and enable individualized prevention and treatment strategies for more people.
Molecular Transducers of Physical Activity

The health benefits of exercise are well documented; scientists have shown that regular physical activity contributes to improved cardiovascular and respiratory health, insulin sensitivity, muscle strength, and mood. However, the precise molecular changes that occur in response to physical activity and the effects these changes have on different tissues and organ systems are poorly understood.

The NIH convened a meeting in October 2014 to identify knowledge gaps and research opportunities that address these questions, and to deliberate ways in which to catalyze coordinated strategies for progress. This meeting and subsequent discussions with the research community helped guide the creation of the Molecular Transducers of Physical Activity Consortium. The consortium is managed by several institutes at the NIH, including the NIDDK, and sponsored by the NIH Common Fund. The consortium’s investigators aim to build an extensive catalogue of biological molecules affected by exercise in people, construct a comprehensive molecular map of these changes, and characterize the functions of these key molecules. The program also aims to create a user-friendly database that researchers can access to aid studies into how exercise promotes better health and prevents disease.

To ensure a broad scope of study, participants will be equally distributed between males and females and will include a variety of ages, racial and ethnic groups, and fitness levels. Throughout the course of the study, both active and sedentary participants will perform different types of exercise, and blood and tissue samples will be collected and analyzed extensively to identify a variety of biological molecules. These analyses will allow for characterization of molecules that are altered at different times during and after physical activity and that could mediate effects on overall health.

In addition to human studies, corresponding studies will be conducted in animal models in order to gather data from cells and tissues affected by physical activity that are not easily studied in humans, such as lung, heart, and brain. The combination of human and animal data will allow researchers to determine how physical activity affects specific molecules in specific tissues at certain times throughout an exercise regimen.

The goal of this program—to determine how physical activity improves health and prevents disease at a molecular level—may contribute to the discovery of new therapeutic targets and could help to provide new approaches to personalized exercise medicine.

For more information on the consortium, please see: https://commonfund.nih.gov/MolecularTransducers/
Workshop on Opportunities for Simulation Research in Gastrointestinal and Urologic Care

On June 10, 2016, the NIDDK and the National Institute of Biomedical Imaging and Bioengineering (NIBIB) co-sponsored a workshop on “Simulation Research in Gastrointestinal and Urologic Care: Challenges and Opportunities,” held on the NIH campus in Bethesda, Maryland. The quality of clinical care available to diagnose and treat gastrointestinal (GI) and urologic diseases depends largely on the expertise of the clinician performing a given procedure, such as an endoscopy or surgery. Like the use of a flight simulator to train airline pilots, training to develop expertise in performing a medical procedure with a successful outcome can be greatly enhanced through use of a simulated experience, which can consist of a computer application, a mannequin or other model, or even a completely simulated surgical environment. Simulation can also help to reduce the number of medical errors made while clinicians are developing a particular procedural skill by lessening their need to “practice” on real patients. Additionally, the use of simulation has the potential to develop the ability to make care more personalized, by allowing a training model to incorporate elements of a person’s unique disease and surgical needs. However, adoption of simulations by training programs for medical personnel has been limited.

The purpose of the workshop was to explore research opportunities for enhancing the adoption of simulation applications by clinicians caring for people with GI and urologic conditions. Presentations by clinicians and scientists in academia and the federal government, as well as others with experience in non-medical fields such as music and sports, highlighted the use of simulation for optimizing training and learning new skills. The speakers also identified recent advances in the field, such as applications for military medicine and the production of more realistic tissue and mannequins, using technologies such as three-dimensional printing. Following the presentations, participants discussed research needs during breakout groups and reported on the groups’ recommendations for addressing gaps and opportunities. A summary of the workshop and its research recommendations has been disseminated broadly throughout the scientific community via publications in two academic journals in the medical literature. The workshop’s recommendations are expected to inform future collaborations by the NIDDK and the NIBIB to address these priorities for enhancing use of simulation in GI and urologic care.