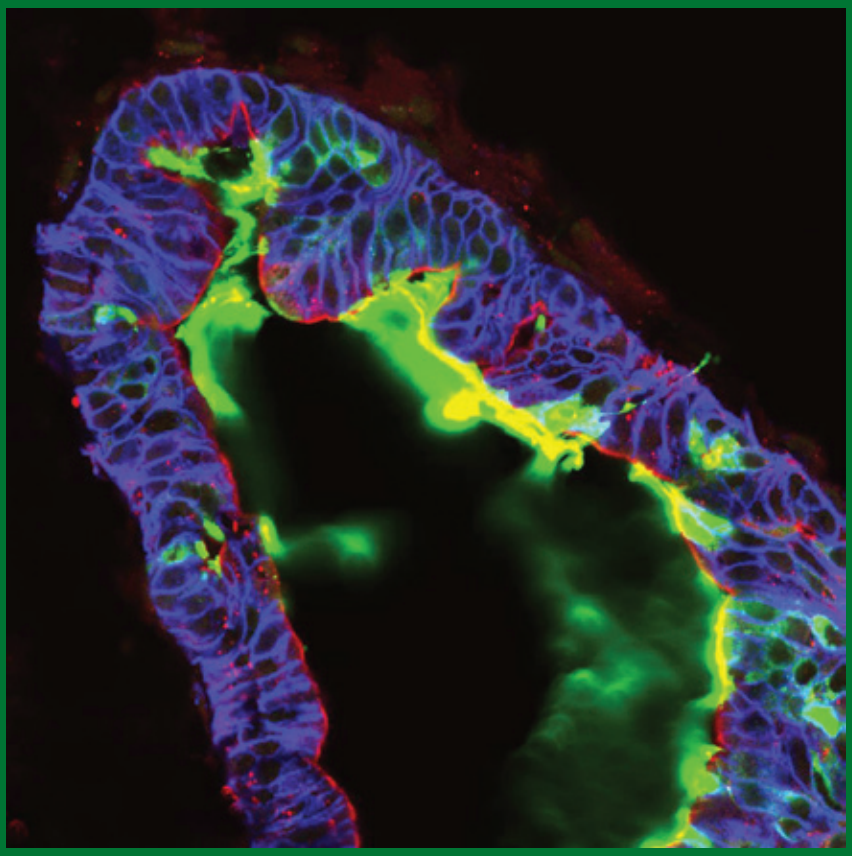

Studies described in this chapter are uncovering the signals that turn stem cells into unique cell types capable of maintaining their identity over multiple cell divisions and even developing into whole tissues in the lab. For example, this image shows a three-dimensional intestinal "organoid," a tissue grown in the lab from stem cells to mimic the structure, cellular complexity, and function of the human intestine. The organoid includes the column-shaped "epithelial" cells found in human intestine (outlined in blue by the presence of a protein called "E-cadherin"). The location of a protein called "villin"—marked in red—on one side of the epithelial cells demonstrates that the organoid epithelial cells are arranged in a manner similar to their organization in the human intestine. Finally, the presence of a protein called "mucin"—shown in green in this image—indicates that the organoid also contains a specialized cell type, which functions as it does in the human intestine by secreting mucin, the major component of intestinal mucus. This pioneering work can help facilitate multiple research directions related to intestinal health and disease, including identifying disease processes, testing new drugs, and regenerating the intestine or generating tissue for transplantation. Other research findings highlighted in this chapter show the promise of related studies on kidney, pancreatic, and blood cells for similar benefits in these tissues.

Image provided by Dr. James M. Wells, and reprinted by permission from Macmillan Publishers Ltd: Nature Methods 8: 111, copyright 2011.

Cross-Cutting Science

Advances in medicine are largely dependent on the accumulation of new knowledge about biologic processes, often at the smallest levels of an organism—its genes, the proteins they encode, the inner workings of cells, and the ways cells communicate with each other. Such basic research discoveries can have broad and far-reaching implications. Major strides in fighting disease can be traced to laboratory studies whose immediate relevance to health could not have been fully known or appreciated at the time they were conducted. Opportunities to make exciting discoveries are arising ever more rapidly with the development of innovative technologies, novel approaches, and even new scientific disciplines as teams of talented, creative researchers join together to pursue increasingly complex challenges. Described in this chapter are several recent studies, whose themes span multiple areas within the NIDDK research mission. The insights gained through this research can be expected to aid progress in many scientific endeavors, for today's research advances may lead to tomorrow's cures.

MAKING A MARK: HOW NIDDK IS ADVANCING EPIGENOMIC RESEARCH

Epigenetics is an emerging frontier of science, relevant to disorders and diseases under the NIDDK mission. This field—the study of changes in gene activity that are not dependent on DNA sequence—is revealing a dynamic layer of regulation in the cell. Chemical modifications to the DNA or on the proteins that package DNA—both of which are called "epigenetic" marks—can silence a gene or turn it on, and these marks alone or in combination lead to exquisite control of gene activity. The ability of an organism to start as a single cell—with a single genome—and derive a multitude of tissues and cells with different functions to become a multi-cellular organism results from these marks. By progressively restricting the activity of gene sets in various tissues and thereby creating, for example, a liver cell or a fat cell, epigenetic marks regulate an organism's development.

Epigenetic marks can be hereditary and long-term or permanent, or can be newly acquired in reaction to a stimulant. The dynamic and responsive nature of epigenetic marks allows for interaction with the environment, whether it's the hormonal or metabolic environment from cellular signals or the outside environment of chemicals, drugs, or diet. By altering the regulation of genes, epigenetic marks could make people more or less susceptible to developing diseases. Therefore, these marks, their regulation, and their function are the focus of many studies related to human development, health, and a variety of diseases and disorders.

To highlight current efforts and stimulate discussion on the NIDDK's role in this field, in February 2011 the NIDDK held a special forum on epigenomics at the meeting of its National Advisory Council. Whereas epigenetics refers to the study of these chemical marks in a single gene or set of genes, epigenomics refers to more global analysis of epigenetic changes across the entire genome. Because of the enormous potential for epigenetic and epigenomic research to enhance understanding of the biological processes of human health and diseases, the NIDDK and NIH support cutting-edge research in this field, including the Roadmap Epigenomics Program, led by several NIH institutes including the NIDDK. This Program supported five research initiatives to transform epigenomics research and launched the Roadmap Epigenomics Mapping Centers, an effort to develop comprehensive epigenome maps for the benefit of the scientific community.

Where the Human Genome Project produced a comprehensive atlas of all the genes in a human cell, the goal of the Roadmap Epigenomics Program is to build a parallel reference of the epigenome, detailing not only where specific chemical marks are found in the genome, but how they vary across healthy cells in different tissues and individuals. With such reference maps, researchers can then ask questions about how the environment or disease alters the epigenome. Such work is not trivial; technological advances in DNA sequencing as well as the ability to detect specific chemical marks were necessary to propel this effort. There are numerous epigenetic marks and the number grows as new ones are discovered. In addition, the researchers are mapping the marks in progenitor cell types, including induced pluripotent stem cells, cell lines, and cells from various human tissues. Already many maps have been generated, allowing researchers to discover how patterns of specific marks vary in different types of cells. More information on the Roadmap Epigenomics Program can be found at *http://commonfund.nih.gov/epigenomics/*

In addition to participating in the Roadmap Epigenomics Program, the NIDDK supports research in this field by extramural investigators in universities and medical centers, as well as within its own Intramural Research Program. While some epigenetic marks are transitory, others are long-term or permanent and need to be passed on faithfully through cell generations. Research presented at the Council forum described results of investigations into how these marks are maintained and passed on during cell division. Scientists are also looking at how proteins involved in gene regulation are influenced, either in activity or location, by these chemical marks. Patterns of epigenetic marks have been used to identify regions of the genome that do not encode proteins, but that do influence gene regulation—regions previously thought to be inactive and called "junk DNA." Seminal research in NIDDK's Intramural Research Program, presented at the Council forum, identified proteins that bind to these regions, revealing that they act to organize the DNA within a cell's nucleus and coordinate gene activity on a genome-wide level. In other efforts, researchers continue to discover new epigenetic marks and probe their effects on gene regulation. Investigators are also now revisiting previously identified areas of the genome associated with complex diseases to determine whether epigenetic marks and patterns are the key to some of these disease associations.

Exciting NIDDK research has begun to reveal some of the promise that epigenomics holds for understanding human health and disease, and new discoveries are expected as research in this field grows. Scientists are working toward cracking the code—discovering all the ways that epigenetic marks influence gene activity—enabling them eventually to read these annotations on the DNA and better predict biological activity. They are riding a tidal wave of new technologies and wealth of information continuing to rise from epigenomic research. Harnessing all this information toward strategies to promote health, prevent disease, and develop new and improved therapies is a goal of NIDDK research. Advances in the Cross-Cutting chapter and the Diabetes, Endocrinology, and Metabolic Diseases chapter in this compendium highlight some of the progress NIDDK-supported researchers are making in the epigenetics of disorders and diseases.

GENERATING NEW TISSUES FROM STEM AND PROGENITOR CELLS—POTENTIAL FOR FUTURE THERAPIES

Scientists Coax Human Pluripotent Stem Cells To Become Three-dimensional Intestinal Tissue: A group of scientists has succeeded in developing a method for turning human adult stem cells that are pluripotent, or capable of becoming any of a number of cell types, into three-dimensional intestinal tissue in culture. Cell culture (laboratory-grown), or *in vitro*, models that reflect the complexity of human tissues could have several health applications, such as understanding developmental and disease processes, as well as testing new therapies. Scientists have determined how to make pluripotent stem cells develop into a single cell type in culture. However, growing a complex tissue like the human intestine, which is composed of multiple layers of unique cell types, in cell culture had thus far eluded them.

Researchers applied their knowledge of key growth factors that drive the differentiation of cells into particular cell types to solving the problem of developing human intestinal tissue in culture. First,

they treated human pluripotent stem cells with a factor called activin A, which caused the cells to form a single layer of tissue similar to the endoderm, a primitive tissue in the developing embryo that later becomes the intestine and other organs. Next, the researchers added a combination of factors called FGF4 and WNT3A, which are important in intestinal development. They found that these factors acted synergistically in guiding the tissue layer to undergo a series of morphologic changes—rolling up into a tube and budding off to form floating "spheroids" with the appearance of miniature intestines. Then the spheroids were transferred to a three-dimensional, gel-based cell culture system that supports intestinal growth. In this milieu, the spheroids changed again into a complex tissue with hallmarks of intestinal epithelium, such as protrusions (villi) on its inner surface. With more time in culture, the tissue became more similar to mature intestinal tissue, displaying a brush border (the brush-like appearance at the tops of some intestinal cells), all of the major cell types of the intestine, and a capacity for nutrient absorption. With their new method, the scientists were able to generate three-dimensional intestinal tissue from several different types of human stem cells. The researchers used this intestinal tissue model to identify molecular pathways contributing to a human genetic condition associated with loss of an intestinal cell type.

This study is the first to show that human pluripotent stem cells can be coaxed to develop into a three-dimensional tissue with features of the human intestine. The impact of this pioneering work has the potential to radiate out in several new research directions, including elucidating pathways involved in inherited intestinal conditions, testing new drugs for their intestinal absorption, and even generating tissue for transplantation in conditions such as inflammatory bowel diseases, necrotizing enterocolitis, and short-gut syndromes.

Spence JR, Mayhew CN, Rankin SA, et al. Directed differentiation of human pluripotent stem cells into intestinal tissue in vitro. Nature 470: 105-109, 2011.

Identification of a Population of Progenitor Cells Capable of Restoring Lost Kidney Function: Scientists have identified a population of progenitor cells in the model organism zebrafish that is capable of forming new filtering units in the kidney following injury.

The nephron is the basic structural and functional unit of the kidney. The cells that comprise the nephron work together to filter blood, removing waste and excess fluid to be excreted as urine. Mammals, including humans, can partly repair damaged nephrons but are incapable of forming new ones. In contrast, fish are able to add new nephrons throughout their lifespan and can regenerate nephrons following injury. In the current study, researchers used zebrafish to study nephron regrowth. Scientists identified small aggregates of cells located throughout the zebrafish kidney that began to proliferate and form new nephrons following drug-induced kidney injury. These progenitor cells were also able to form new nephrons after being transplanted into other fish. Furthermore, real-time imaging of nephron formation in transparent zebrafish larvae showed that the aggregates form when multiple progenitor cells come together and then differentiate into nephrons.

Overall, the process of nephron formation in the zebrafish following injury was similar to that seen in mammalian kidney development. These findings suggest that, if such progenitor cells exist in mammalian kidneys, it might be possible to identify and activate them following nephron loss. The development of a regenerative therapy to restore kidney function in patients with kidney injury or chronic kidney disease would have a significant impact on patient care and well-being.

Diep CQ, Ma D, Deo RC, et al. Identification of adult nephron progenitors capable of kidney regeneration in zebrafish. Nature 470: 95-100, 2011.

New Information on How To Make and Maintain Beta Cells: Scientists discovered important steps in the development and maintenance of insulin-producing beta (β) cells. Loss of β cell function plays a role in both type 1 and type 2 diabetes. Therefore efforts to develop functional β cells are important for both forms of the disease. While scientists have made great strides toward generating β cells from stem cells in the laboratory for cell therapies and research, this goal has not yet been achieved. Two studies have made further headway toward this goal by revealing the roles that chemical marks on the genome play in instructing cells to become and remain β cells, and restricting them from other possible cell fates.

In one study, researchers investigated whether there are early chemical marks on the proteins that package DNA that guide certain cells in a choice between becoming pancreas or liver. They examined liver- and pancreas-specific genes in multipotent mouse cells—cells that have the ability to become many types of cells. In these multipotent cells, the liver and pancreas genes are not active, but the scientists found that liver and pancreatic genes have distinct and different "prepatterns" of the chemical marks, depending on whether the cells will go on to become liver or pancreas cells. These marks may help predict which multipotent cells are poised to become β cells, or be a target to coax multipotent cells to become β cells—both of which could help scientists generate β cells in the laboratory.

In the second study, researchers examined whether a specific chemical mark on DNA, known as "methylation," was important to maintain a β cell's identity. Researchers genetically altered mice to lack a protein in β cells responsible for this mark. This led to a loss of β cells and an increase in another pancreas cell type, the α cell. The scientists demonstrated that these new α cells derived from dividing β cells, and that the methylation mark is important to block activation of a gene that would promote α cell development. This discovery—of a mark critical to maintaining β cell identity—provides a new opportunity to promote β cell development. Insights from these two studies arm scientists with critical information toward producing β cells in the laboratory. By manipulating these marks, scientists may be able to coax cells to become and remain β cells.

Xu C-R, Cole PA, Meyers DJ, Kormish J, Dent S, and Zaret KS. Chromatin "prepattern" and histone modifiers in a fate choice for liver and pancreas. Science 332: 963-966, 2011.

Dhawan S, Georgia S, Tschen S, Fan G, and Bhushan A. Pancreatic β cell identity is maintained by DNA methylation-mediated repression of Arx. Dev Cell 20: 419-429, 2011.

Wnt—the Multitasker: Three new studies are providing key insights into the role of the Wnt signaling pathway in several different biological processes: blood stem cell production, regeneration of new bladder cells following injury, and growth of cells in the kidney.

All blood cell types are derived from a population of self-renewing hematopoietic (blood) stem cells (HSCs) that first appear during embryonic development. As *Wnt* genes have been identified as having an important role in some aspects of embryogenesis, researchers sought to better understand the role of Wntl6—a member of the Wnt signaling pathway—in the formation of HSCs. In the first study, researchers examined zebrafish and found that a reduction of the levels of Wnt16 protein during early stage embryonic development blocked the production of HSCs. The results indicate that Wntl6 is required for the production of HSCs during zebrafish development; given that the gene shows similar patterns of expression in mice, it is possible that it has a similar function in mammals.

When the bladder is invaded by bacteria, it initiates a counter-attack, shedding the innermost layer of cells in contact with urine in an effort to prevent invading bacteria from getting a foothold on underlying cells deeper within the bladder wall. Within 24 hours of bacterial infection in mice, remaining bladder cells begin to divide to replenish cells that have been shed. The second study identified a positive feedback loop whereby the bladder cells signal to underlying stromal cells following injury, and the stromal cells stimulate the bladder cells to divide. This growth signal is mediated through Wnt pathways.

Waste removal in the kidney occurs in tiny units called nephrons. During kidney development, the nephron progenitor cell population needs to be precisely controlled to ensure the formation of the appropriate number of nephrons. In the third study, researchers demonstrated in mice that the Wnt9b signaling pathway is active in progenitors and is required for their renewal and proliferation. Wnt9b influences nephron development in conjunction with the transcription factor Six2. When Six2 is present, Wnt9b directs the progenitor cell to remain a progenitor; when Six2 levels are diminished, Wnt9b induces the progenitor cell to develop (differentiate) into a nephron. Thus, the kidney uses Wnt to pre-load a developmental process that is then modulated by the levels of Six2.

Together, these reports provide important information about fundamental molecular and cellular signaling

processes in cell development, growth, and response to injury.

Clements WK, Kim AD, Ong KG, Moore JC, Lawson ND, and Traver D. A somitic Wntl6/Notch pathway specifies haematopoietic stem cells. Nature 474: 220-224, 2011.

Shin K, Lee J, Guo N, et al. Hedgehog/Wnt feedback supports regenerative proliferation of epithelial stem cells in bladder. Nature 472: 110-114, 2011.

Karner CM, Das A, Ma Z, et al. Canonical Wnt9b signaling balances progenitor cell expansion and differentiation during kidney development. Development 138: 1247-1257, 2011.

WHEN THE BODY ATTACKS ITSELF—RESEARCH ON SMALL MOLECULES TO TREAT AUTOIMMUNE DISEASE

Identification of New Class of Compounds That Suppress Autoimmunity: Scientists have developed a novel small molecule that suppressed onset and reduced severity of an autoimmune disease in a mouse model. Autoimmune diseases result from a misguided attack against the body's own organs, tissues, or cells launched by the immune system. These diseases differ in how they manifest; for example, in inflammatory bowel diseases, the misguided immune system action leads to inflammation in the intestines, while in multiple sclerosis, the protective coating that surrounds nerve cells is attacked. Because these diseases result from inappropriate activity of the immune system, current treatments for some autoimmune diseases suppress both harmful and protective aspects of the immune system. These treatments can have toxic side effects and increase a person's risk for infection. Scientists, therefore, are pursuing therapies to more selectively repress specific cells involved in autoimmunity.

In a recent advance, a multidisciplinary team of researchers developed a small molecule, called SR1001, which selectively affects T_H17 cells—immune system cells that have been previously implicated in autoimmune diseases. They demonstrated that SR1001 binds to and represses two proteins, called RORα and RORγt, whose activity is required for the development of T_H17 cells. The scientists discovered that SR1001 inhibited the development of certain mouse cells into T_H17 cells. In addition, when they added SR1001 to existing mouse and human T_H17 cells, they observed a decrease in activation of genes linked to T_H17 cell function.

The scientists also tested whether SR1001 treatment had an effect on a mouse model of multiple sclerosis—one of several autoimmune diseases in which T_H17 cells are known to play a role. Treatment with SR1001 suppressed the clinical severity and onset of autoimmunity in these mice. Importantly, SR1001 was found to target T_H17 cells and not other immune cells, suggesting that the compound may provide a specific way to suppress disease-causing cells without generally suppressing the immune system. Scientists will need to investigate whether SR1001 has potential side effects beyond the immune system and whether it has utility in human disease, but these exciting results identify a new class of compounds—SR1001 and related molecules—that have promise in the treatment of autoimmune diseases.

Solt LA, Kumar N, Nuhant P, et al. Suppression of T_H17 differentiation and autoimmunity by a synthetic ROR ligand. Nature 472: 491-494, 2011.

Potential New Treatment for Graves' Disease: Scientists have identified a small molecule that inhibits the unregulated cellular signaling that gives rise to Graves' disease, also known as toxic diffuse goiter. Graves' disease is the most common cause of overactive thyroid (hyperthyroidism) in the United States. Hyperthyroidism occurs when the thyroid gland makes more thyroid hormone than the body needs. Current treatment choices include radioiodine therapy, surgery, or drugs that block thyroid hormone action and can have rare, but serious, toxicity. The gland makes two hormones, triiodothyronine and thyroxine, that affect nearly every part of the body: metabolism, brain development, heart and nervous system functions, bowels, body temperature, muscle strength, skin and hair, menstrual cycles, weight, and cholesterol levels. Thyroid hormone production is regulated by another hormone called thyroid-stimulating hormone (TSH), which is made by the pituitary gland in the brain. Graves' disease is an autoimmune disease, in which the immune system makes thyroid-stimulating antibodies that activate the TSH receptor (TSHR). These abnormal antibodies mimic the action of TSH and stimulate the thyroid to make too much thyroid hormone.

In new research, scientists synthesized and tested several small molecules, and identified one that directly blocks thyroid-stimulating antibodies from activating the TSHR. The small molecule, called NCG00229600, appears to act by binding to a site on the TSHR independent of where the thyroid-stimulating antibodies (and TSH) bind—an "allosteric" site. Once bound, it most likely prevents antibody-induced changes in the shape of TSHR, which would be required for receptor activation. To test whether NCG00229600 could inhibit signaling by the TSHR, the scientists used two different cell types: an established cultured cell line with high levels of TSHR and cells isolated from human thyroid tissue. They incubated these cells with blood samples that had been collected from 30 individuals with Graves' disease. These blood samples contained the disease-associated thyroid-stimulating antibodies. In the cultured cell line, the presence of NCG00229600 inhibited TSHR signaling by 39 percent; in the thyroid cells, the level of inhibition was 65 percent. NCG00229600 has not yet been tested in clinical trials with people who have Graves' disease, but this exciting research has opened up a new avenue for possibly treating this chronic disease.

Neumann S, Eliseeva E, McCoy JG, et al. A new small-molecule antagonist inhibits Graves' disease antibody activation of the TSH receptor. J Clin Endocrinol Metab 96: 548-554, 2011.

MAPPING THE CELL: PROTEIN STRUCTURE AND GENETIC REARRANGEMENTS

Scientists Paint a "High-Definition" Picture of a Cell Surface Signaling Protein: A detailed description of the three-dimensional structure of the A_{2A} adenosine receptor has shed new light on one of the fundamental elements of how cells in the body communicate with each other. The detailed structure of this receptor was determined to a resolution finer than 3 angstroms—a unit of measurement that is 1/10,000,000,000 (one ten-billionth) of a meter in length. (By way of comparison, a common house fly is approximately 60 million angstroms long.)

To detect and respond to signaling molecules, cells often employ specialized proteins on their surface termed "receptors." Once a signaling molecule binds, the receptor initiates a cascade of events that results in a cellular response. Signaling through the receptor for the molecule adenosine plays an important role in a diverse array of biologic processes, from playing a key role in cardiovascular physiology to mediating coffee's caffeine-driven "buzz." Adenosine receptors are members of a particularly complex family of lengthy proteins that zig-zag back and forth across the cell membrane a total of seven times—the "7TM" receptors. The precise physical and biochemical changes that these receptors undergo upon binding various activators and inhibitors remain a largely unresolved question. In part, this is because their unusual structure has made these proteins poorly suited for traditional methods that have been used to probe structure/function relationships in biomolecules.

While all receptors in the 7TM family share a similar overall structure, there are significant differences among them in several regions, which are hypothesized to contribute to the different responses each receptor elicits when activated. In the current study, the researchers isolated and crystallized a form of the A_{2A} adenosine receptor bound to a synthetic activator. (There are four related receptor subtypes for adenosine.) They described how three of the seven membrane-spanning segments of the receptor tilt, rotate, shift, and "see-saw" when bound to the activator, as compared to their orientation in its absence. Additionally, when the activator was present, one loop of the extracellular portion of the A_{2A} adenosine receptor shifted in a way that the researchers hypothesize is specific to this member of the 7TM family. This enhanced understanding of basic structural and functional changes of the receptor when it is bound to an activator represents a key contribution to researchers' knowledge of this family of molecules. It also demonstrates that it is possible to obtain a stable, activator-bound form of a 7TM receptor at high resolution, which will be helpful in future studies of other members of this family.

Xu F, Wu H, Katritch V, et al. Structure of an agonist-bound human A_{2A} adenosine receptor. Science 332: 322-327, 2011.

A New Map Drives Studies of Genetic Rearrangement: Scientists discovered key features of hotspots associated with genetic rearrangement—the

process by which cells intentionally break, shuffle, and repair their DNA to create new combinations of genes. Genetic rearrangement occurs naturally in cells destined to become sperm and eggs to generate genetic diversity, ensuring that each organism is unique. This process can be beneficial in that new advantageous traits can arise from these genetic rearrangements, but if it goes awry, this process can also generate abnormalities that result in miscarriages, congenital birth defects, and mental retardation. Scientists had known that genetic rearrangements occur more frequently at certain locations in the genome—"hotspots"—but they did not know what makes these locations hotspots. Previous studies focused on individual hotspots, but to determine the common features of mammalian hotspots scientists needed a way to map all of the hotspots in an organism. Researchers in NIDDK's Intramural Research Program developed a molecular approach to identify and catalog hotspots in mice, and generated a high-resolution physical map of these sites in the mouse genome. This map allowed them to identify common characteristics of the mapped hotspots, such as a tendency for hotspots to be found in genes, to be associated with a complex of proteins that package DNA (nucleosomes), and to have a sequence similar to that of the binding site for a protein, called PRDM9, that modifies nucleosomes. The scientists went on to find that hotspots were associated with the specific nucleosome modification produced by PRDM9, hinting at how the process of genetic rearrangement unfolds. In addition to providing a powerful new tool for studies of genetic rearrangement, these findings have the potential to improve the detection of genes linked to disease and to help understand the causes of genetic abnormalities.

Smagulova F, Gregoretti IV, Brick K, Khil P, Camerini-Otero RD, and Petukhova GV. Genome-wide analysis reveals novel molecular features of mouse recombination hotspots. Nature 472: 375-378, 2011.

Dr. David T. Breault and Dr. Jose C. Florez: NIDDK-Supported Scientists Receive Presidential Award

In September 2011, President Barack Obama recognized 94 U.S. scientists, including two supported by the NIDDK, as recipients of the 2010 Presidential Early Career Awards for Scientists and Engineers (PECASE; *www.whitehouse.gov/the-press-office/2011/09/26/president-obama-honors-outstanding-early-career-scientists)*.

PECASE is the highest honor bestowed by the U.S. government on science and engineering professionals in the early stages of their independent research careers. Awardees are selected for their innovative research and their commitment to community service demonstrated through scientific leadership, public education, or community outreach.

Among the 2010 recipients are David T. Breault, M.D., Ph.D. and Jose C. Florez, M.D., Ph.D., both NIDDK extramural grantees.

In addition to Drs. Breault and Florez, 18 other NIH-supported scientists received the award for their research achievements. The NIH has now funded 193 PECASE recipients since the award's inception in 1996. A list of NIH scientists who have received this prestigious award is available at *www.grants.nih.gov/grants/policy/pecase.htm*

Characterizing Intestinal Stem Cell Populations

David T. Breault, M.D., Ph.D.

Dr. Breault, a pediatric endocrinologist at Children's Hospital Boston and Harvard Medical School, received a 2010 PECASE award for his research characterizing a subpopulation of intestinal stem cells in mice with unique reparative properties identified using an innovative biomarker. In humans and mice, the lining of the digestive tract undergoes continuous and rapid renewal throughout life, which is sustained by stem cells located within indentations in the intestinal surface called "crypts." This renewal is critical to repopulate lost cells and maintain a barrier against the potentially harmful contents of the digestive tract. In the absence of this renewal, the intestinal tissue may become diseased or inflamed. Therefore, scientists like Dr. Breault are studying intestinal stem cells for clues that could lead to the development of novel therapies for these conditions. Dr. Breault and his colleagues studied a mouse genetically modified so that cells with the biomarker, a specially tagged version of a cellular component called telomerase, are visible under a fluorescent microscope. Telomerase adds special caps to the ends of chromosomes, to protect the cell's genetic material, and is particularly important for cells that must continue to divide, such as stem cells. With this mouse model, Dr. Breault and his colleagues identified a slowly dividing stem cell subpopulation within intestinal crypts. Interestingly, this subpopulation is resistant to injury and contributes to the regenerative response following this injury, suggesting that it may have therapeutic potential. The results of Dr. Breault's pioneering research studying this cell population and its regulatory pathways may give rise to novel therapeutic strategies for gastrointestinal diseases, such as inflammatory bowel diseases, short bowel syndrome, and intestinal cancer.

Learning How Genetics Has an Impact on the Efficacy of Diabetes Drugs

Jose C. Florez, M.D., Ph.D.

Dr. Florez, a geneticist and endocrinologist at Harvard Medical School, received a 2010 PECASE award for his studies to characterize genetic loci associated with type 2 diabetes and related traits in an effort to advance individualized therapy. Although a number of genetic loci have been associated with type 2 diabetes, in many cases the identity of the causal gene and understanding of how it affects disease risk and treatment remain unknown. Dr. Florez's research employs an innovative strategy combining state-of-the-art pharmacogenetic (the study of how genetics influences a drug response) and metabolomic (the study of molecules involved in metabolism) approaches in human studies. In a current study, Dr. Florez and his colleagues will measure the effects of two different diabetes medications—glipizide and metformin—in people at risk for diabetes or with diet-treated diabetes and compare the responses of people who have differences in genetic variants associated with diabetes. In a previous study of the genetics of participants in the NIDDK's Diabetes Prevention Program, Dr. Florez's group found that metformin was ineffective in preventing diabetes in individuals with two copies of a common variant of the *SLC47A1* gene, which encodes a protein that transports metformin, while it was effective for prevention in those with one or no copies of the variant. In addition to furthering understanding of the biology of glucose regulation and how drugs affect the disease, Dr. Florez's research aims to provide new insight into how genetic variants have an impact on an individual's diabetes risk and personalized treatment.