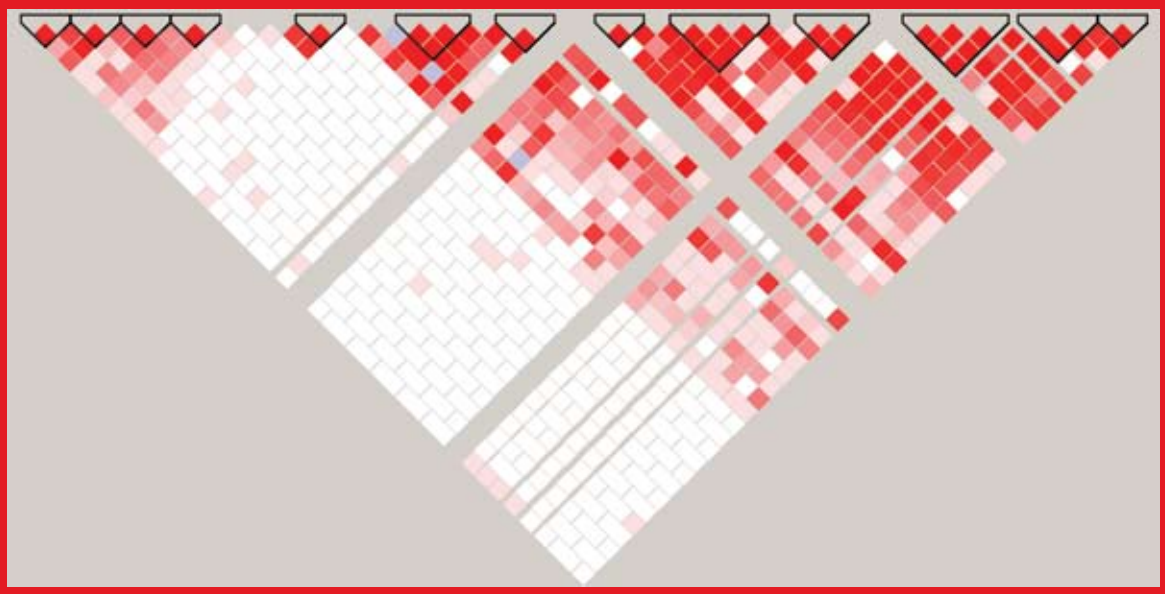


A genome-wide association study involves rapidly scanning markers across the genome to find genetic variations associated with a particular disease. Scientists conducting these studies analyze genetic differences between people with a particular disease and healthy people. As described in this document, recent genome-wide association studies have led to the identification of key genes involved in a variety of diseases within the NIDDK's mission. This image shows data from a genome-wide association study conducted to identify genes involved in inflammatory bowel disease. Understanding which genes contribute to disease not only enhances understanding of the underlying causes of disease, but could illuminate new targets for prevention and therapy.

Image provided by Dr. John Rioux and reprinted by permission from Macmillan Publishers Ltd: Nature Genetics, 39: 596-604, copyright 2007.

Cross-Cutting Science

Advances in medicine are largely dependent upon the accumulation of new knowledge about biologic processes, especially at the smallest levels of an organism—its genes, the proteins they encode, and the workings of cells. While the ultimate application of such basic research is not always obvious, major strides in fighting disease can be traced back 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 new discoveries and advances are arising ever more rapidly with the development of new technologies, new approaches, and even new scientific disciplines. Described here are some recent studies of fundamental processes, ranging from the development of cells to the development of organisms, and new approaches and technologies that make such studies possible. The insights gained through this type of research can be expected to propel disease-oriented research, not only within the NIDDK mission, but also in many other fields. Investment in such cross-cutting scientific research today will have future applications that we cannot now describe with certainty, but which we know will surely be realized.

GENOME-WIDE ASSOCIATION STUDIES

A new era is beginning in the search for genes that contribute to disease. With the completion of the Human Genome Project and the International HapMap Project, scientists now have a set of research tools that make it possible to find genes that influence the likelihood of developing common diseases. Genome-wide association studies rely on these newly-available research tools and technologies to identify genetic differences between people with specific illnesses and healthy individuals. Through this comparison, it becomes possible to identify even subtle genetic differences between affected and unaffected people. This approach allows scientists to study diseases that involve many different genes, such as diabetes and inflammatory bowel disease.

To perform a genome-wide association study, scientists rapidly scan the genomes of many people for markers, called single nucleotide polymorphisms (SNPs). SNPs are single variations in the sequence of nucleotides or letters in the DNA code (A, T, G, and C). These variations occur in all people and most often are not associated with disease. To find SNPs that are associated with a particular disease, researchers compare many thousands of SNPs among people with and without disease, and identify candidate SNPs that are found significantly more or less often in one of the two groups. Such disease-associated SNPs can serve as strong pointers to regions of the genome where genetic risk factors reside. The first variants detected often do not directly influence disease susceptibility; however, the actual causal variant may lie nearby. This means researchers often need to take additional steps, such as sequencing every DNA base pair in that particular region of the genome, to identify the exact genetic variant that affects disease risk.

As described elsewhere in this edition of *NIDDK Recent Advances and Emerging Opportunities*, genome-wide association studies have already led to novel discoveries about genes involved in diseases within the NIDDK mission. For example, researchers have identified four new genetic variants associated with increased risk of type 2 diabetes and confirmed the existence of another six variants. This research brings to 10 the total number of genetic variants confidently linked to risk for the disease. Two of the newly-identified variations are in genes or regions not previously known to play a role in biological processes involved in diabetes. Their discovery opens new avenues of research for treatment or prevention of the disease. In addition, genome-wide association studies have led to the discovery of a new gene associated with type 1 diabetes. The gene is primarily expressed

in cells of the immune system and therefore may play a role in the immune system's attack of insulin-producing beta cells leading to type 1 diabetes onset.

Also described in this compendium are recent research advances from the NIDDK's Inflammatory Bowel Disease Genetics Consortium. Using genome-wide association studies, the Consortium identified several new genes and chromosomal regions associated with Crohn's disease. For example, the interleukin-23 (IL-23) receptor is a major susceptibility gene; the gene variant actually protects people against the development of Crohn's disease. They also identified *ATG16L1*, which is involved in a process (autophagy) used to degrade damaged cellular components and to help eliminate some pathogenic bacteria. The communities of bacteria that normally reside in the gut have been associated with Crohn's disease, so it will be interesting to see what role the new gene may play.

The NIDDK continues to support other genome-wide association studies. For example, ongoing studies are using samples collected from type 1 diabetes patients and their family members in the Epidemiology of Diabetes Interventions and Complications (EDIC) study and the Genetics of Kidneys in Diabetes (GoKinD) study. Scientists are using these well-defined collections to search for genetic variations associated with the development of long-term diabetes complications. Thus, the NIDDK is building on past investments in research and taking advantage of new and emerging technologies to pursue novel directions and gain new scientific information.

Why is it important to find genes that contribute to disease? Once new genetic associations are identified, scientists can use the information to learn more about the underlying cause of disease. For example, a gene could encode a protein that is involved in a signaling cascade with numerous other proteins. This knowledge could illuminate several new therapeutic targets for disease prevention or treatment. Furthermore, newly-identified genetic associations could be completely unexpected, as was the case for some type 2 diabetes genes. These types of surprising findings lead to brand new avenues for research that would likely not have been pursued otherwise. Therefore, even though the identification of new disease-associated genes is exciting in and of itself, the research sets the stage for even more scientific breakthroughs.

GENES AND THE ENVIRONMENT

New genomics technologies enable scientists to address questions of enormous complexity and importance, and genetic data are a key component in identifying and characterizing factors that influence health. However, the role of the environment should not be overlooked. Research initiatives at both the NIH and NIDDK levels aim to illuminate the intertwined roles played by genetic predisposition and environmental influences in the development and progression of disease.

The NIDDK is participating in an effort led by the National Human Genome Research Institute called the "Genes, Environment and Health Initiative" or GEI. This effort represents collaboration between geneticists and environmental scientists. It will use innovative genomic tools as well as new instruments for measuring the environmental factors themselves—from diet and physical activity to stress and substance addiction—in order to begin sorting out how these different factors affect a person's risk for a number of health conditions. To identify the genetic risks, researchers will use the rapidly evolving technologies used in genome-wide association studies to focus on common conditions, such as heart disease, cancer, and diabetes. The environmental component will begin by developing new technologies that accurately measure personal exposures with small, wearable sensors that can be used to assess environmental agents. The final component of the research strategy is to determine whether the effect of genetic variants that increase disease risk is different in the presence of environmental exposures.

In addition to this NIH-wide effort, the NIDDK is also supporting studies that address the role of genetics and environment in diseases within its research mission. "The Environmental Determinants of Diabetes in the Young" study is designed to solve this equation for type 1 diabetes, in which one or more as-yet unidentified environmental triggers spark autoimmune destruction of the body's insulin-producing cells. The hope is that a vaccine or change of diet, for example, could one day prevent the disease in those at risk. The project may also provide key insights on environmental causes of celiac

disease, which has overlapping genetic susceptibility with type 1 diabetes.

In celiac disease, gluten—a major protein in wheat, rye, and barley—triggers an immune response that damages the small intestine and interferes with the absorption of nutrients. Microbes that live in the human gut represent a key part of our body's internal environment. Recent NIDDK-supported research has established that there is bidirectional induction of genes between the body and intestinal bacteria, influenced by other environmental factors, such as nutrients. Future NIDDK efforts seek to expand understanding of the genomes of the gut bacteria—the microbiome—and detail the microbes' impact on human health. As discussed below, the NIDDK is also involved in the Human Microbiome Project, a new initiative recently launched as part of the NIH Roadmap. This project is aimed at more fully characterizing the human microbiome, and seeks to generate resources that will enable analysis of the role of the microbiome in human health and disease.

The new NIDDK Metabolic Clinical Research Unit at the NIH Clinical Research Center will permit intramural and extramural scientists an unprecedented opportunity to take environmental, dietary, and metabolic snapshots of normal, overweight, or obese patients. The facility will be an excellent resource for studies aimed at improving our understanding of the gene-environment interaction as it affects metabolic health, as well as for answering other research questions pertinent to obesity and overweight.

Another effort to tie environmental variables to metabolic health outcomes is an initiative on the obese and diabetic intrauterine environment. This initiative seeks to shed light on long-term impact on children born to mothers who were obese and/or diabetic during their pregnancies. Together, these examples of NIDDK research into these interactions promise to greatly increase our understanding of this critical interface between genes and the environment.

NIH ROADMAP FOR MEDICAL RESEARCH: SECOND COHORT OF ROADMAP PROGRAMS

The NIH Roadmap for Medical Research is an "incubator space" for nascent programs that cut across the NIH in terms of relevance or complexity, and which no single Institute or Center can address completely. The NIH Roadmap is now entering a new phase of scientific endeavor. Following the development of the first generation of Roadmap initiatives from inception to transition out of the incubator space, a second cohort of Roadmap programs is now in development. The new initiatives are being developed under the auspices of the Office of Portfolio Analysis and Strategic Initiatives (OPASI), a trans-NIH coordination and planning structure recently created within the NIH Office of the Director. While the new Roadmap initiatives are cross-cutting in nature, many of them intersect with NIDDK mission areas and could greatly aid research progress.

The second cohort of Roadmap initiatives began as ideas generated in Summer and Fall of 2006 by a wide range of stakeholders in the intramural and extramural scientific community, the patient advocacy community, and the general public. OPASI coordinated a review of the scientific concepts submitted and relevant NIH portfolios—applying criteria that potential Roadmap initiatives should meet. For example, Roadmap initiatives must be truly transforming; outcomes should synergize with missions of individual NIH Institutes and Centers to promote health; and trans-NIH participation must be required to address a scientific area in which no single NIH entity is likely to engage. Directors of the NIH Institutes and Centers then selected the areas, and the specific initiative concepts, that could be pursued. NIDDK representatives have participated in several of the Working Groups charged with developing these concepts.

Two concepts were approved as major Roadmap initiatives to be implemented immediately as 5-year programs: the Human Microbiome Project and the Epigenomics Program. The Human Microbiome Project aims to characterize the microbial content of sites throughout the human body and examine whether changes in the "microbiome" (including the collection of microbial species and their genetic material) are related to disease. The NIDDK Director serves as a co-leader of this Project, which will develop new tools and reference sequence data needed to study the human microbiome. Because the gastrointestinal (GI) tract is home to the body's largest collection of microbes, the Human Microbiome Project could greatly aid efforts to understand microbial effects on digestive health and disease.

The Epigenomics Program will develop resources for research in this area, which focuses on genetic modifications that change gene expression and function without altering the DNA sequence. This research will characterize the "epigenome" (a catalog of the stable epigenetic changes that occur in the genome) and its impact on health and disease. Plans include the creation of an international consortium, development of reference epigenomes, and establishment of a publicly available epigenetic database, as well as other research resources. In addition, support will be provided for fundamental discovery of novel epigenetic "marks"—marks on the chromosomes that activate or silence particular genes. Epigenetics may provide a mechanism by which environmental factors, such as diet, contribute to diseases such as type 2 diabetes and GI cancers. The NIDDK has therefore taken an active role in the Epigenomics Working Group, and serves as the lead Institute for the discovery initiative.

In the case of the two new Roadmap initiatives that will proceed to implementation, the release of Requests for Applications (RFAs) for 5-year programs began in Fall 2007, with awards to be made in Summer 2008 through Fiscal Year 2009. In addition to the immediate implementation of the Microbiome and Epigenetics Programs, other initiatives are being further developed for possible future implementation. These include a Phenotyping Services and Tools initiative, which was developed with leadership provided in part by the NIDDK Director. This initiative will develop a catalogue of human phenotypes for characterization of complex diseases. For the Protein Capture Tools/ Proteome Tools initiative, tools and resources will be developed to identify and isolate all proteins in the human body (the proteome). A pilot study will create a Genetic Connectivity Map—an effort to discover commonalities in gene expression patterns among diseases, responses to drug candidates, and genetic manipulations.

While these new Roadmap initiatives and pilot studies go forward, Roadmap Coordination Working Groups will continue to assess current efforts and future opportunities for cross-cutting collaborations in regenerative medicine, pharmacogenomics, and bioinformatics. The ongoing focus of the Roadmap Strategic Planning Working Groups will be on research training and research career development, health disparities, and effective administrative approaches to fostering scientific research.

More information on the second cohort of Roadmap programs can be found at:
http://nihroadmap.nih.gov/roadmap15update.asp

STEM CELLS, PROGENITOR CELLS, AND DISEASE APPROACHES

Stem cells have the potential to develop into many different cell types in the body. To better understand these cells and "progenitor cells," which have a more limited developmental potential, scientists continue to characterize their properties and seek potential new ways of using them to benefit patients.

Stem Cell Studies Provide New Insight into Aging: Clues about diseases associated with the aging process are beginning to emerge from studies of stem cells produced in the bone marrow. New investigations are helping close the gap in knowledge about these stem cells, including aspects of their microenvironment and factors that influence them in their primitive state or that control their activation and differentiation. For example, researchers have wondered why stem cells in the bone marrow of mice become less able to divide and replenish the supply of blood cells as they age. One theory proposed that, over time, these stem cells develop genetic mutations—but this idea has not been widely endorsed because these cells rarely divide. Hence, they are not thought to be susceptible to DNA damage, which is believed to be responsible for most mutations during cell division—mutations that may accumulate and give rise to cancer. To determine whether these stem cells accumulate genetic damage as they age, researchers recently isolated some cells from the bone marrow of normal young and old mice and indirectly determined the extent of their DNA damage. The cells from young mice showed no damage, whereas those from older animals showed extensive damage. In a different set of experiments, the researchers showed that mice with mutations in genes involved in DNA repair did not lose stem cells with age. However, the stem cells from these animals were much less effective in colonizing the depleted bone marrow of irradiated mice (which are similar to mice that have undergone a bone marrow transplant procedure) compared to

normal stem cells. This finding is consistent with the hypothesis that accrual of DNA damage may contribute to the diminished capacity of older animals to maintain health following stress or injury. These results could help to explain the development of leukemia and immune disorders that occur as people age.

Rossi DJ, Bryder D, Seita J, Nussenzweig A, Hoeijmakers J, and Weissman IL: Deficiencies in DNA damage repair limit the function of haematopoietic stem cells with age. Nature 447: 725-729, 2007.

Potential New Stem Cell Approach to Transplantation: In another study, researchers developed a potential new approach to using stem cells for transplantation. Genetically matched embryonic stem (ES) cells are a potential source of cells and tissues for transplantation. Ideally, cells for transplantation will be well-matched with the recipient's cells in terms of proteins expressed on the cell surface, in order to minimize or prevent a response by the host's immune system. Most, if not all, ES cells are isolated from fertilized embryos. In an attempt to improve the degree of tissue matching, scientists isolated ES cells from an unfertilized mouse egg through a process called parthenogenesis, thus omitting the sperm's genetic contribution. The scientists identified stem cell lines retaining the identical "self" genetic information of the mouse egg donor and transplanted the cells into their respective donor for up to three months. The transplanted cells gave rise to tissues that were not rejected by the immune system of the donor mouse. While this research is very preliminary, the technique could offer an alternative method for deriving tissue-matched human ES cells that would not require destruction of a fertilized embryo.

Kim K, Lerou P, Yabuuchi A, Lengerke C, Ng K, West J, Kirby A, Daly MJ, and Daley GQ: Histocompatible embryonic stem cells by parthenogenesis. Science 315: 482-486, 2007.

Liver Regeneration from Bone Marrow Stem Cells: Researchers have uncovered an important clue to the cellular origins of the regenerating liver—one that comes from outside the organ itself, in the bone marrow. The liver has a remarkable ability to return to its original size after injury, resection of diseased tissue, and/or transplantation with a piece of donor tissue. Improved understanding of the source of the cells involved in repopulating the liver can inform the use of future cell-based therapies, as well as enhance fundamental knowledge of the organ's developmental and regenerative processes. Past research identified stem cells residing within the adult liver, called oval cells, as an important source of cells for the regenerating liver. However, conflicting reports existed regarding whether these oval cells originated from inside or outside the liver—namely, in the bone marrow. NIDDK-supported scientists recently conducted a series of animal experiments that strengthened the case for bone marrow-derived cells under certain conditions. In these studies, rats were given a chemical to inhibit expansion of cells within the liver, so that any observed liver regeneration could be attributed to cells from outside the organ. The rats then received a bone marrow transplant from a "donor" rat and underwent a surgical or chemical procedure to trigger liver regeneration. The transplant donor differed from the recipient in both genetics and gender. The genetic difference enabled researchers to observe donor bone marrow cells that had migrated to the liver during regeneration and became oval cells, then differentiated into mature liver cells. By providing a way to count the number of X chromosomes present, the gender difference between donor and recipient allowed scientists to determine that the oval cells had directly matured into liver cells, rather than simply fused with mature liver cells. Based on these findings, the researchers concluded that, in conditions of severe liver injury and inhibition of cells inside the liver, bone marrow cells may play an important role in regenerating the liver. Together with other studies, this work adds to the evolving understanding of the complex, multiple pathways controlling liver regeneration. Further research on the cellular regeneration pathway between the bone marrow and the liver has the potential to lead to useful cell-based therapies for liver disease.

Oh SH, Witek RP, Bae SH, Zheng D, Jung Y, Piscaglia AC, and Petersen BE: Bone marrow-derived hepatic oval cells differentiate into hepatocytes in 2-acetylaminofluorene/partial hepatectomy-induced liver regeneration. Gastroenterology 132: 1077-1087, 2007.

Intestinal Stem Cells Lacking Tumor Suppressor Promote Polyp Formation: In laboratory studies, researchers have delineated how normal stem cells transition to cancer stem cells that can initiate the

formation of tumors in the intestine. In humans, the lining of the digestive tract undergoes continuous and rapid renewal throughout life. This renewal is sustained by a population of stem cells located in small recessed areas called crypts. These cells are "multipotent," which means that they are capable of developing into more than one cell type of the body. Although it has been known that the development of numerous polyps in the intestine results primarily from an abnormal increase in the number of crypts, the underlying cause remained unknown. Intestinal polyps are generally benign growths (non-cancerous) but some polyps can progress to cancer. To gain new insights, researchers studied a conditional knock-out mouse model, in which the tumor suppressor gene known as *PTEN* was deleted in the intestine. They determined that the deficiency in PTEN results in both an increase in number and an altered distribution of the stem cell population. The excess stem cells drive new crypt formation, which eventually results in formation of polyps. These findings offer opportunities to further characterize cancer stem cells—knowledge that will inform future cancer therapy studies.

He XC, Yin T, Grindley JC, Tian Q, Sato T, Tao WA, Dirisina R, Porter-Westpfahl KS, Hembree M, Johnson T, Wiedemann LM, Barrett TA, Hood L, Wu H, and Li L: PTEN-deficient intestinal stem cells initiate intestinal polyposis. Nat Genet 39: 189-198, 2007.

Colonic Stem Cell Markers and Regulatory Pathways: The recent identification of genes turned on specifically in regions of the colon containing stem cells has provided new insight into the molecular signals important for the healthy renewal of colonic cells. Cells of the human colon are renewed about once every week, as stem cells located in the bottom folds of the colon called "crypts" mature and migrate to the top of the colon surface, where differentiated cells perform key digestive functions. In order to understand the signals that differ between frank colonic cells and those that can develop into one of a number of cell types, researchers dissected the colon into a "top" (surface) and a "bottom" (crypts) section and looked for genes that were expressed exclusively in one area. When dividing the colon tissue this way, the researchers were able to include all the cells that play a supporting role in contributing signals to the stem cells and differentiated cells. As was expected, the differentiated top portion of the colon expressed genes that inhibit cell proliferation and genes that are required for digestive functions. Genes involved in cell proliferation and renewal were specifically turned on in the deeper, undifferentiated portion of the colon tissue. The contribution of several previously identified cell signaling pathways to the unique character of cells in the top versus bottom colon was examined as well. The researchers found that signaling through pathways involving molecules known as Wnt and Notch, which often regulate stem cell fate and early tissue development, was characteristic of the crypts of the colon. Bone morphogenetic protein (BMP) signals, typically activated during cell differentiation, were characteristic of the top portion of the colon. In contrast, BMP signaling was blocked in the crypt region by the presence of naturally occurring BMP antagonists produced by the supporting cells. The activity of these antagonists was found to activate Wnt signaling, inhibiting differentiation and promoting stem cell self-renewal and expansion in the crypts. These results extend to humans previous findings in mice, and elucidate the roles of different signaling pathways and molecules in creating an environment necessary for appropriate colon cell renewal. By further understanding the biology behind cell renewal in the colon, scientists may be able to develop therapeutics to stimulate or block these signals as needed when they go awry, such as in colon cancer.

Kosinski C, Li VSW, Chan ASY, Zhang J, Ho C, Tsui WY, Chan TL, Mifflin RC, Powell DW, Yuen ST, Leung SY, and Chen X: Gene expression patterns of human colon tops and basal crypts and BMP antagonists as intestinal stem cell niche factors. Proc Natl Acad Sci USA 104: 15418-15423, 2007.

Identification of Gastric Stem Cells: Recently, researchers have discovered a cell population in the stomach with stem cell-like properties that may be involved in renewal of tissue, as well as tumor formation. To date, gastric stem cells have not been well-characterized due to a lack of specific cell markers to identify them within the tissue and to assist in their purification. In this study, researchers identified a marker to visualize these rare cells and to trace them to a specific region of the mouse stomach predicted to harbor stem cells. The areas suspected to contain these rare cells were the gastric glands, which are located at the base of pits on the interior surface of the stomach. These stem cells were able to proliferate and repopulate the entire gland with multiple cell types, indicating

that all the cells in the gland have the stem cell as their single source. Interestingly, expansion of these stem cells could be triggered by a pro-inflammatory molecule, suggesting that they could respond to injury within the stomach by replacing the injured cell types. However, the stem cells were also located in an area where gastric tumors commonly form, raising the possibility of their involvement in this process. These studies provide evidence for the importance of these newly recognized gastric stem cells in the maintenance and renewal of stomach tissue, and highlight their potential role in gastric cancer development. This initial characterization provides the experimental tools necessary for further studies to explore the properties of this unique stem cell population within the stomach.

Qiao XT, Ziel JW, McKimpson W, Madison BB, Todisco A, Merchant JL, Samuelson LC, and Gumucio DL: Prospective identification of a multilineage progenitor in murine stomach epithelium. Gastroenterology 133: 1989-1998, 2007.

Identification of Progenitor Cell Protein Involved in Pancreas Development: Scientists have identified a protein that is required for maintaining a pool of progenitor cells in the pancreas. Progenitor cells are cells destined to form a particular tissue or organ, such as the pancreas. As cells specialize, they often lose their ability to divide and make new cells. Progenitor cells that give rise to specialized cells generally maintain the ability to divide and can replenish lost specialized cells. Thus, research on progenitor cells is key to achieving the major goal of developing a means of growing unlimited quantities of insulin-producing beta cells in the laboratory. Such cells could be transplanted into people with type 1 diabetes to treat their disease. This goal is extremely challenging because it requires understanding the complex signaling pathways that are necessary to grow progenitor cells and induce them to become beta cells. Researchers made strides toward this goal with the discovery that a protein called SOX9 is necessary for maintenance and expansion of tissue specific precursors that give rise to the beta cell and other pancreatic cells. When they examined SOX9 expression in pancreatic cells during different stages of mouse embryonic development, the protein was found to be expressed in pancreatic progenitor cells, but not in more differentiated cell types. To examine SOX9's role in pancreatic development, mouse embryos were generated that lacked the protein in tissues that would normally form the pancreas. These mice did not develop normal pancreases, had extremely high blood sugar levels, and died within the first 4 days of life. Their rudimentary pancreases did not produce pancreatic hormones, such as insulin or glucagon. These results suggest that SOX9 is required for normal pancreas growth and cellular differentiation. Further studies indicated that SOX9 helps maintain the pancreatic progenitor cell pool by stimulating the cells' proliferation and survival. It is not yet clear whether SOX9 is involved in helping replenish stores of beta cells in adults, or is only involved during embryonic development. This research has enhanced understanding of pancreas development, which could inform the development of methods to grow insulin-producing beta cells in the laboratory for use in cell-based therapies for diabetes.

Seymour PA, Freude KK, Tran MN, Mayes EE, Jensen J, Kist R, Scherer G, and Sander M: SOX9 is required for maintenance of the pancreatic progenitor cell pool. Proc Natl Acad Sci USA 104: 1865-1870, 2007.

New Insights into Mouse Stem Cell Markers with Implications for Tissue Renewal: Therapies to regenerate diseased or injured organs will require an in-depth knowledge of how stem cells and progenitor cells develop into complex tissues and organs. For example, by developing methods specifically to recognize pancreatic progenitor cells, scientists will be better able to purify and grow these cells for transplantations to treat patients with diabetes or pancreatic disorders. In a recent study using a rodent model, researchers examined over 1,100 genes to determine which were expressed at key stages early in mouse pancreatic development, thereby potentially revealing genetic markers specific to pancreatic progenitor cells. Using this approach, the team found that the developing pancreas consists of five discrete domains of progenitor cells. They found and characterized one of these domains that was poised at the key position where progenitor cells branched into the three major functional cell types of the pancreas—hormone producing cells, including insulin-producing beta cells; digestive enzyme producing cells; and ductal cells that transport these digestive enzymes to the gut. Using the new markers they identified, the researchers were able to visualize the progression of these "multipotent" progenitor cells and their progeny within the mouse tissue into the

different pancreatic cell types. The ability to observe the changes in tissue location of these progenitor cells during development provided insight into how these cells physically populate the tissue of the pancreas. In a related effort to understand biological regulation of how a more general stem cell type—a mouse embryonic stem cell—develops into a broader array of tissues, scientists examined new and known stem cell markers to understand the relationship among these molecules. The researchers were able to create a map showing how the molecules influence and regulate one another. A thorough understanding of all stem cell markers will help scientists understand the natural development of tissues, and will be crucial for attempts to use these cells to repopulate injured or diseased tissues in humans.

Zhou Q, Law AC, Rajagopal J, Anderson WJ, Gray PA, and Melton DA: A multipotent progenitor domain guides pancreatic organogenesis. Dev Cell 13: 103-114, 2007.

Zhou Q, Chipperfield H, Melton DA, and Wong WH: A gene regulatory network in mouse embryonic stem cells. Proc Natl Acad Sci USA 104: 16438-16443, 2007.

Contrasting Developmental Programs in the Pancreas and Liver: Researchers have identified a fundamental difference in the way the pancreas forms during development compared to other organs, such as the liver. Working with mice, the scientists studied pancreatic progenitor cells. When the researchers selectively eliminated all the pancreatic progenitors from mouse embryos, each resulting mouse was born without a pancreas. When they eliminated some, but not all of the progenitors, the mice were born with smaller pancreases that never grew to normal size. In contrast, selective elimination of a large fraction of liver progenitor cells did not significantly affect the ultimate size of the mouse liver, presumably because the embryonic mice were able to rapidly compensate by creating more progenitor cells from a pool of pre-existing liver stem cells. These results imply that there are two types of organs—those whose size is determined by the number of progenitor cells that arise during development, and those whose size is controlled by different cues and resident stem cell populations. The experiments are also consistent with the observation that, while the adult human liver is capable of significant regeneration when damaged, the pancreas is much more limited in its ability to re-grow. From the standpoint of clinical research, the results indicate underlying developmental parameters that should be considered or circumvented in strategies for treating pancreatic damage resulting from injury or diseases such as diabetes.

Stanger BZ, Tanaka AJ, and Melton DA: Organ size is limited by the number of embryonic progenitor cells in the pancreas but not the liver. Nature 445: 886-891, 2007.

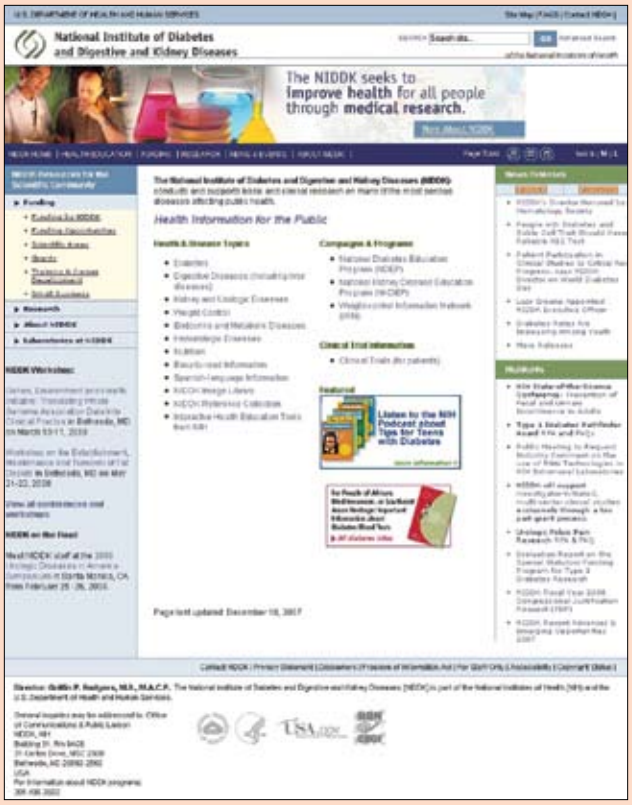
The New Public Face of NIDDK

In this "high-tech" era, more and more people use the Internet to access information. In particular, the NIDDK's website (*www.niddk.nih.gov*) receives nearly 2 million visitors each month. The NIDDK website is the public face of the Institute and is important for disseminating the many informational resources that the NIDDK has to offer.

In 2007, the NIDDK unveiled a new and improved website. The new design changed the look and feel of the website to be more appealing to visitors, but the high quality and fundamental architecture of information were preserved. Changes to the website include colorful graphics that help to convey NIDDK's science and public health mission, a new layout that is easier for visitors to navigate, and new features that highlight news and events.

The website still contains links to important health information for patients, families, and healthcare providers on diseases and disorders within the NIDDK mission. It also has information for scientists, such as information on research funding opportunities and research resources. Much information is tailored to specific groups of scientists, such as postdoctoral fellows and newly-independent investigators. The redesigned website makes it easier for these many different audiences to find the information that they are looking for in a timely and efficient way. In a press release announcing the launch of the new website, Dr. Griffin Rodgers, NIDDK Director, said: "Our new design should save researchers, health professionals, and the public valuable time finding important scientific and consumer health information. We are continually striving to make our resources more readily available to a wider audience and in the latest formats. The website plays a key role in helping to disseminate this information."

Please visit the new NIDDK website at *www.niddk.nih.gov*



The newly-designed NIDDK website: *www.niddk.nih.gov*