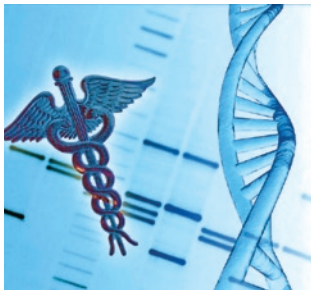
News and Resources from the National Institutes of Health

Digestive Diseases
NEWS
National Digestive Diseases Information Clearinghouse
Spring/Summer 2008

Genomics Research Yielding Personalized Approach to IBD Treatment



Doctors may soon consider a person's genes when treating inflammatory bowel disease (IBD) and other conditions. This new, personalized approach is possible through the translation of genomics research into clinical practice, a process recently discussed at a 2-day meeting at the National Institutes of Health (NIH) in Bethesda, MD.

"Translation is something that moves discovery into health practice: from the bench to bedside in the first stage and then from the bedside to the general public," said National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Director Griffin P. Rodgers, M.D., M.A.C.P., who set the stage for the meeting "Genes, Environment, and Health Initiative (GEI): Translating Whole Genome Association Data into Clinical Practice."

Genome-wide association studies compare the genetic profiles of healthy individuals with those with specific health conditions. Such studies have uncovered at least 30 genes related to IBD and others involved in diseases such as diabetes, cancer, and heart disease. Improved strategies for gene hunting and cheaper sequencing techniques are quickening the pace of discovery, helping scientists develop new diagnostic tools and strategies and target-specific therapeutics.

Gene-Environment Interactions

The GEI was launched in 2006 by U.S. Department of Health and Human Services Secretary Michael O. Leavitt to help understand how genes and environmental exposures influence health and disease. Most common health conditions are thought to arise from complex gene-environment interactions (GxE). For fiscal year 2007, $40 million for the GEI was added to $28 million the NIH already had slated for GxE research. The first grants were announced in September 2007.

"We are at an interesting juncture," National Human Genome Research Institute Director Francis S. Collins, M.D., Ph.D, told meeting attendees. "The amount of discovery that has occurred in the area of genetics of common diseases is breathtaking and the challenge now is to try to build upon that."

IBD is a chronic, painful condition resulting from inflammation of the gastrointestinal tract. Crohn's disease and ulcerative colitis are the two

Genomics Research,
continued on page 2

Inside This Issue

NIDDK
National Institute of Diabetes and Digestive and Kidney Diseases

"The amount of discovery that has occurred in the area of genetics of common diseases is breathtaking and the challenge now is to try to build upon that."

Francis S. Collins, M.D., Ph.D
National Human Genome Research Institute Director

Genomics Research, from page 1

major types of IBD. Diverse clinical features of Crohn's and ulcerative colitis have been linked to multiple genes—some of which appear to be interacting with each other and environmental factors, such as smoking—suggesting IBD is not one or two diseases but many.

Judy Cho, M.D., associate professor of medicine and genetics at the Yale University School of Medicine, highlighted successes of the NIDDK IBD Genetics Consortium, including the discovery of variants of the gene that encodes for IL-23R, a receptor found on immune cells that triggers inflammatory pathways in response to bacteria. Specifically, IBD is believed to result from an inappropriate immune response to nonpathogenic bacteria in the gastrointestinal tract.

Cho, the principal investigator of the Consortium's data coordinating center, said identifying genes that regulate these immune responses has been enormously helpful in understanding the pathophysiologic mechanisms contributing to IBD and the development of much-needed new therapeutic interventions.

The NIDDK IBD Genetics Consortium includes the

- Cedars-Sinai Genetics Research Center, Los Angeles
- Johns Hopkins Genetics Research Center, Baltimore
- University of Pittsburgh Genetics Research Center
- University of Montreal Genetics Research Center
- The University of Toronto Genetics Research Center
- Yale University Genetics Research Center, New Haven, CT

The NIDDK IBD Genetics Consortium, established in 2002, coordinates analysis of IBD genetics data collected by six American and Canadian research centers. See the box for a list of participating centers.

Improved Outcomes

"Very potent biologics, in particular the development of monoclonal antibodies against TNF, have profoundly improved the outcomes of patients with inflammatory bowel disease," said Cho. "However, these new biologics can be associated with significant infectious complications." Monoclonal TNF antibodies, used in the biologic treatments infliximab (Remicade) and adalimumab (Humira), interrupt the inflammatory process in IBD by blocking TNF, a proinflammatory cytokine.

In addition, not all people with IBD will benefit from taking these new therapies. "There is a group of people with IBD that does very well on new anti-TNF biologics for IBD," said Stephan Targan, M.D., director of the Inflammatory Bowel Disease Center at the Cedars-Sinai Medical Center in Los Angeles. "But there is a group that doesn't do so well—in fact, some people don't even respond."

Targan believes genomics data will help doctors identify people at increased risk of IBD and better match patients with effective drugs. "A patient-specific treatment will be dialed in based upon the different pathways that may be associated with different IBD subtypes."

For more information about IBD, see the NIDDK fact sheets about Crohn's disease and ulcerative colitis under the A to Z list of topics and titles at *www.digestive.niddk.nih.gov*.

Digestive Diseases
NEWS

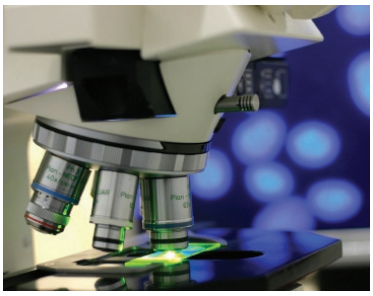
Digestive Diseases News, an email newsletter, is sent to subscribers by the National Digestive Diseases Information Clearinghouse (NDDIC). The newsletter features news about digestive diseases, special events, patient and professional meetings, and new publications available from the NDDIC and other organizations.

If you would like to subscribe, go to *http://catalog.niddk.nih.gov/newsletter.cfm*. You can read or download a PDF version of the newsletter at *http://digestive.niddk.nih.gov/about/newsletter.htm*.

Executive Editor: Stephen P. James, M.D.

Dr. James is the director of the Division of Digestive Diseases and Nutrition within the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). As director, Dr. James oversees planning, implementation, and evaluation of a national research effort focused on gastrointestinal, pancreatic, hepatobiliary, and nutrition diseases and conditions. Before joining the NIDDK in 2001, Dr. James directed the division of gastroenterology at the University of Maryland's School of Medicine for 10 years.

Genes Affect Natural Immune Response to Hepatitis C Virus



Genes affecting the activity of natural killer (NK) cells—immune cells that destroy virus-infected cells—vary widely in the population and may explain why some people are more likely to clear the hepatitis C virus (HCV) from their bodies while others are more likely to develop chronic disease.

About 75 percent of people infected with the hepatitis C virus develop chronic disease, which can lead to cirrhosis of the liver, liver cancer, and liver failure.

"There appears to be a certain degree of natural immunity in a small subset of individuals," Barbara Rehermann, M.D., told attendees of the National Institutes of Health (NIH) Directors' Seminar entitled "Host Factors Involved in the Control of Hepatitis C Infection."

Rehermann, who heads the immunology section of the National Institute of Diabetes and Digestive and Kidney Diseases' (NIDDK) Liver Diseases Branch, cited data from epidemiological genetics studies led by Mary Carrington, Ph.D., at the National Cancer Institute (NCI), which showed an association between recovery from hepatitis C infection and a distinct gene pattern. People who recovered shared similar gene variations affecting the killer cell immunoglobulin-like receptors (KIRs) on NK cells and their ligand human leukocyte antigen (HLA-C), located on target cells. *KIR/HLA-C* interactions are known to dictate cell targeting by NK cells, but how genetic variations might enhance NK cell activity was unclear.

Sparked by this observation, Rehermann studied the effect of *KIR/HLA-C* gene combinations on NK cell function in a lab-based virus infection model. Using blood samples from healthy blood donors with defined *KIR/HLA-C* gene variants, Rehermann determined that when exposed to virus-infected target cells, the immune response of NK cells from individuals with genes for type 1 HLA-C was more rapid and robust than that of NK cells taken from individuals with genes for type 2 HLA-C. Rehermann's results were published in the March 2008 *Journal of Clinical Investigation*.

Because NK cells provide a first line of defense against viral pathogens, these results suggest NK cells play a pivotal role during the initial stages of a virus infection.

Crucial Collaboration

Access to a seemingly endless supply of genetically defined cell samples through collaboration with the NCI group was crucial to the study. "I am convinced that this could not have been done at any other place," said Rehermann. "This is why it is so interesting to be at the NIH."

About 75 percent of people infected with the hepatitis C virus develop chronic disease, which can lead to cirrhosis of the liver, liver cancer, and liver failure. Hepatitis C affects 500 million people worldwide and is the leading cause of liver transplantation in the United States.

"The projected prevalence of HCV-related liver disease in the United States alone is expected to quadruple within the next 30 years," said Rehermann. "The future prediction does not look so good," she added, highlighting the need for better immune modulatory therapies.

The NIDDK's National Digestive Diseases Information Clearinghouse has more information about hepatitis C at *www.digestive.niddk.nih.gov/ddiseases/pubs/hepatitis*. To view a videocast of Rehermann's lecture, visit *www.videocast.nih.gov/PastEvents.asp?c=25*. ■

Work on Digestive Diseases Research Plan Continues

After more than 2 years of work, the National Commission on Digestive Diseases made significant progress toward completing a 10-year plan to guide digestive diseases research at the National Institutes of Health (NIH) during its meeting in May.

In the plan, the Commission identifies digestive diseases research opportunities that span basic, translational, and clinical science settings, including clinical trials in children, adults, and special populations such as high-risk groups or the disadvantaged.

The 16-member Commission's recommendations are the result of extensive advice and input from investigators and advocates in multiple areas of digestive diseases. Commission members, who were appointed by NIH Director Elias A. Zerhouni, M.D., include extramural researchers from academic institutions across the United States, medical professionals, and patient advocates. The members formed 12 working groups to develop the topic-specific chapters of the plan, calling on additional external experts to provide input.

Stephen P. James, M.D., director of the Division of Digestive Diseases and Nutrition at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), chairs the Commission. The NIDDK is the lead entity for coordinating digestive diseases research at the NIH.

The public had an opportunity to review and comment on the plan between February 8 and March 8, 2008. Comments from stakeholder organizations, the Commission's ex-officio members, and concerned lay and professional representatives "were highly appreciative and complimentary," said James. The comments enhanced the research plan by leading to the generation of a number of new research goals and objectives.

In the plan, the Commission identifies digestive diseases research opportunities that span basic, translational, and clinical science settings, including clinical trials in children, adults, and special populations such as high-risk groups or the disadvantaged. The Commission also identifies challenges to optimal implementation of the research plan and proposes cross-cutting, innovative scientific directions, technologies, and resources that would promote progress in digestive diseases research.

More than 70 million Americans are affected by digestive diseases annually at a price tag of nearly $100 billion in direct medical costs. In fiscal year 2007, 20 NIH Institutes, Centers, and Offices spent more than $1.2 billion to support digestive diseases research.

For more information about the Commission and the 10-year plan, go to *www2.niddk.nih.gov/AboutNIDDK/CommitteesAndWorkingGroups/NCDD/default.htm.* ■

NIH Lecture Series Spotlights Liver Cancer, Transplantation, and Organ Allocation

The increasing rate of liver cancer in the United States has focused attention on the shortage of donor livers for people who need them—and how decisions are made about who gets them. These issues were the subject of a recent session in the Demystifying Medicine lecture series at the National Institutes of Health (NIH).

Liver transplantation and tumor removal are the only currently effective options for treating liver cancer, which has been increasing in the United States due to growth of the hepatitis C virus and the Asian population in this country, according to Irwin Arias, M.D., moderator for the lecture series designed for doctoral students, fellows, and staff.

A study of nearly 700 individuals with liver cancer found that half had hepatitis C, 15 percent had hepatitis B, and 5 percent had both. Another study associated diabetes with a two-fold increase in the risk of liver cancer, according to Arias. Other risk factors for liver cancer include obesity, alcohol, hemochromatosis, and aflatoxin.

The 1-year patient survival rate among people who have received liver transplants is 85 to 90 percent, according to Marc Ghany, M.D., a gastroenterologist with the National Institute of Diabetes and Digestive and Kidney Diseases' Liver Diseases Branch who participated in the lecture. The 3-year survival rate is 75 to 80 percent, and the 8-year survival rate is 60 to 70 percent, Ghany said. Currently, about 17,000 people are on a waiting list for a donated liver. About 1,800 people on the list die before receiving one.

Allocating Limited Resources

According to criteria from the United Network for Organ Sharing (UNOS), an individual's position on a waiting list for a liver depends on blood type, waiting list time, mortality risk score—or the probability of death without a transplant—and whether the individual is a child, according to Alan Wertheimer, Ph.D., a research scholar in the department of bioethics at the NIH Clinical Center. In his lecture, Wertheimer explored whether the UNOS policy is ethical and how scarce medical resources should be allocated in the United States.

To view the lecture entitled "Liver Cancer: A Global Problem. Who Gets the Liver Transplant?" go to *http://videocast.nih.gov/summary.asp?file=14460*. The NIH launched the Demystifying Medicine lecture series to help bridge the gap between advances in biology and their application to major human diseases.

The 2-hour lectures are held on the NIH campus from January through May and are presented live through online streaming video. Recorded videos are available online following each live event. For more information about Demystifying Medicine lectures, visit *www1.od.nih.gov/oir/DemystifyingMed*. ■

NIDDK Welcomes Four New Advisory Council Members

U.S. Department of Health and Human Services Secretary Michael O. Leavitt appointed four new members to the Advisory Council of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The Advisory Council guides the NIDDK's discussion of broad science policy issues and provides second-level review of funding requests. The new members, who will serve 4-year terms, are

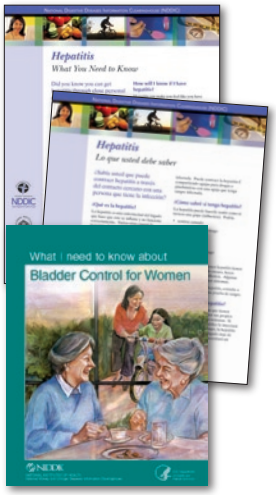
David M. Altshuler, M.D., Ph.D., professor of genetics and medicine at Harvard Medical School, member of the Diabetes Unit and Department of Molecular Biology at Massachusetts General Hospital, and director of the Program in Medical and Population Genetics at the Whitehead Institute/Massachusetts Institute of Technology Center for Genome Research in Boston. Altshuler serves on the Diabetes, Endocrinology, and Metabolic Diseases Subcommittee.

Nancy C. Andrews, M.D., Ph.D., dean and vice chancellor of Academic Affairs at Duke University School of Medicine in Durham, NC. She is the only woman to lead one of the nation's top 10 medical schools and is an internationally renowned researcher in pediatric hematology and oncology. Andrews serves on the Kidney, Urologic, and Hematologic Diseases Subcommittee.

James W. Freston, M.D., Ph.D., the Boehringer Ingelheim Chair of Clinical Pharmacology and professor emeritus at the University of Connecticut School of Medicine at Farmington. Appointed to the NIDDK Advisory Council last year for a 1-year term, Freston has been reappointed this year for a 4-year term. He continues to serve on the Digestive Diseases and Nutrition Subcommittee.

Pictured with NIDDK Director Griffin P. Rodgers, M.D., M.A.C.P. (center), are (from left) Nancy C. Andrews, M.D., Ph.D.; James P. Schlicht, M.P.A.; James W. Freston, M.D., Ph.D.; and David M. Altshuler, M.D., Ph.D. Photo credit: Michael Spencer, NIH.

James P. Schlicht, M.P.A., executive vice president and chief government affairs and advocacy officer at the American Diabetes Association (ADA). He is directly responsible for management of all advocacy and government affairs functions and the formulation, adoption, strategic development, and implementation of all ADA public policy positions. Schlicht serves on the Diabetes, Endocrinology, and Metabolic Diseases Subcommittee. ■



NIDDK Publications Win NIH Plain Language Awards

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) received recognition in this year's National Institutes of Health (NIH) Plain Language Awards Competition.

The NIDDK Awareness and Prevention Series was honored with a gold award and the easy-to-read booklet *What I need to know about Bladder Control for Women* won a bronze. An awards ceremony was held at the NIH campus in Bethesda, MD, on April 15.

The NIDDK Awareness and Prevention Series, created for health fairs and similar events, presents brief overviews in English and Spanish of common health problems in a colorful, two-page format. Designed for people not yet diagnosed with diabetes or digestive, kidney, or urologic disorders, the handouts encourage readers to seek further information from the NIDDK or their health care provider.

The *What I need to know about Bladder Control for Women* booklet explains treatments and techniques for managing urinary incontinence and helps women prepare to speak with their doctors about the problem.

The NIH created the Plain Language Awards to promote the NIH Plain Language Initiative, established in response to a 1998 White House memorandum calling for all Federal Government writing to be in an easy-to-read format. The booklet and Awareness and Prevention Series publications can be downloaded or ordered through the NIDDK website at *www.niddk.nih.gov*.

Resources

Featured in the NIDDK Reference Collection

Colonic Polyps

The review article "Colonic Polyps in Children and Adolescents" notes that colonic polyps in children most commonly present with rectal bleeding. The article considers colonic polyps in children and adolescents, covering isolated juvenile polyps, juvenile polyposis syndrome, familial adenomatous polyposis, attenuated familial adenomatous polyposis (AFAP), and mutY homologue *(MYH)*-associated polyposis. Juvenile refers to the histological type of polyp and not the patient's age at polyp onset. Adolescents and adults with multiple juvenile polyps are at significant risk of developing intestinal cancer. Both adult and pediatric gastroenterologists must try to determine the risk of colorectal cancer in people with juvenile polyposis syndrome. AFAP can occur either by a mutation at the extreme ends of the *adenomatous polyposis coli* gene or by biallelic mutations in the *MYH* gene. The identification of *MYH*-associated polyposis as an autosomal recessive condition has important implications for screening and management strategies.

The article concludes with a brief discussion about compliance with surveillance recommendations and future directions. "Colonic Polyps in Children and Adolescents" was published in the April 2007 issue of the *Canadian Journal of Gastroenterology*.

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Reference Collection is a free, online database that helps health care professionals, health educators, patients, and the general public find educational materials not typically referenced in most databases. To find more digestive diseases resources, visit *www.catalog.niddk.nih.gov/resources*.

Additional Resources

Updated Fact Sheets

The National Digestive Diseases Information Clearinghouse has updated the following fact sheets:

- *Autoimmune Hepatitis*
- *Barrett's Esophagus*
- *Diverticulosis and Diverticulitis*
- *El aparato digestivo y su funcionamiento (Your Digestive System and How It Works)*
- *Intestinal Pseudo-obstruction*
- *Wilson Disease*

These publications are available at *www.digestive.niddk.nih.gov/ddiseases/a-z.asp*.

New Interactive Tools

New to the Interactive Health Education Tools section of the NIDDK website are

Podcasts

- State-of-the-Science Conference: Fecal Incontinence

Videocasts

- Host Factors Involved in the Control of Hepatitis C Virus Infection
- Prevention of Fecal Incontinence in Adults (Days 1 through 3)
- Demystifying Medicine—Inflammatory Bowel Diseases: What Is the Target?

The website's interactive tools section consolidates all the tools and resources about digestive diseases from the National Institutes of Health and the National Library of Medicine. To access these resources, visit *www.digestive.niddk.nih.gov/resources/HealthTools*.

Nuclear Receptors in Liver and Digestive Diseases

A report of a workshop about nuclear receptors in liver and digestive diseases was published in the March 2008 issue of *Cell Metabolism*. The workshop, sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), convened scientists to review state-of-the-art knowledge of nuclear receptors; promote cross-fertilization among basic, translational, and clinical investigators; and integrate the understanding of nuclear receptor biology and current clinical challenges for a variety of digestive and liver disease states. The report concludes that scientists need a better understanding of nuclear receptor expression in individual cell types that comprise tissues, including cells with mostly metabolic functions, those with central roles in injury and inflammation, and, particularly, stem cell populations given their increasingly recognized role in disease and tissue repair.

Acute Liver Failure

A summary of a workshop about acute liver failure (ALF) sponsored by the NIDDK in December 2006 was published in the April 2008 issue of *Hepatology*. Emergency liver transplantation is the only proven effective therapy for ALF. The NIDDK workshop focused on better understanding and managing the disease and developing recommendations for future research. ■

Upcoming Meetings, Workshops, and Conferences

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) will exhibit at the following upcoming conferences:

American Academy of Family Physicians Scientific Assembly

September 17 to 21 in San Diego.
For more information, go to *www.aafp.org/online/en/home/cme/aafpcourses/conferences/assembly.html*.

American College of Gastroenterology Annual Scientific Meeting and Postgraduate Course

October 3 to 8 in Orlando, FL.
For more information, go to *www.acg.gi.org/acgmeetings*.

American Academy of Pediatrics 2008 National Conference and Exhibition

October 11 to 14 in Boston.
For more information, go to *www.aapexperience.org*.

American Dietetic Association Food and Nutrition Conference and Expo

October 25 to 28 in Chicago.
For more information, go to *www.eatright.org/cps/rde/xchg/ada/hs.xsl/events.html*.

American Academy of Nursing 35th Annual Meeting and Conference

November 6 to 8 in Scottsdale, AZ.
For more information, go to *www.aannet.org/i4a/pages/index.cfm?pageid=3577*.

Drug-induced Liver Injury

The NIDDK is sponsoring a workshop about drug-induced liver injury on December 1 to 2, 2008, in Bethesda, MD. The workshop will evaluate current diagnostic criteria and means of assessing causality in drug-induced liver injury and attempt to standardize nomenclature, clinical measurements, causality instruments, and definitions of outcomes. Poster abstract submissions are due by Friday, October 3. For more information about the workshop entitled "Drug-Induced Liver Injury: Standardization of Nomenclature and Causality Assessment," go to *www3.niddk.nih.gov/fund/other/diliworkshop2008*. ■

NIH Publication No. 08–4552
July 2008