UCLA Health

Beyond the Scope

A REPORT OF THE UCLA DIVISION OF DIGESTIVE DISEASES

FALL 2014

FROM THE DIVISION CHIEFS

Gary Gitnick, MD
Fran and Ray Stark Foundation Chair
Professor of Medicine

Eric Esrailian, MD, MPH
Lincy Foundation Chair in Clinical Gastroenterology
Associate Clinical Professor of Medicine

Going **Beyond** the Scope

UCLA's Division of Digestive Diseases is dedicated to its mission of advancing the scientific knowledge and understanding of digestive disorders. Through discoveries in our laboratories and their translation to novel diagnostic and therapeutic approaches, we make improvements in care that are relieving suffering and enhancing quality of life for patients all over the world.

To be truly successful in this aspect of our mission, we must fulfill another critical calling – education of the researchers and clinicians of tomorrow and today. This includes the physicians in the community who are in a position to take advantage of the knowledge we obtain to provide better care for their patients.

With that in mind, the UCLA Division of Digestive Diseases is proud to offer two major education programs back to back – what we refer to as **UCLA GI Week**. On March 12, 2015, the Center for Ulcer Research and Education (CURE) Annual Research Meeting and Poster Session will be held. This daylong meeting sponsored by the CURE: Digestive Diseases Research Center is comprised of lecture presentations and an extensive poster session and prominently features the work of young investigators.

The rest of that week – March 13-15, 2015 – we are delighted to present the 3rd Annual UCLA-Mellinkoff Gastroenterology and Hepatology Symposium. Whereas the CURE meeting showcases the latest in scientific discovery, the UCLA-Mellinkoff Symposium represents two-and-a-half days of approaches and solutions that physicians can readily integrate into their daily practices. Named after our Division's first chief, Sherman M. Mellinkoff, this lively and informative symposium highlights current practice and future trends of GI and liver disorders (see pages 8-11).

In this issue of *Beyond the Scope,* we highlight some of the exciting discoveries that are being made in Division laboratories. Two of these involve inflammatory bowel diseases (IBD). A group led by Dr. Sang Hoon Rhee has identified a combination of genetic mutations that appear to work together to cause many cases of pediatric ulcerative colitis. In the process, Dr. Rhee's group has created a first-of-its-kind animal model that can be used to test new drug candidates for the disease (see page 2). Another group, this one headed by Dr. Georgios Koukos, has uncovered a specific non-coding RNA that appears to play an important role in causing pediatric ulcerative colitis (see page 4). Dr. Koukos and colleagues present evidence strongly suggesting that the responsible pathway is epigenetically regulated, which opens the door to new ways of studying IBD.

This issue also takes a step back to look at the remarkable 40-year history of our CURE: Digestive Diseases Research Center, which has evolved from its initial purpose of solving the once-enormous problem of gastric ulcer – and CURE was instrumental in doing just that – into a multidisciplinary research center that continues to lead the way on the most important digestive diseases issues of the day (see page 1).

We hope you find this and all issues of *Beyond the Scope* to be informative, and that you will consider attending UCLA GI Week to learn more. Education is as important as anything we do, for we are well aware that the critical contributions our Division makes to advancing knowledge through research is of little value unless that knowledge is disseminated to the wider scientific and medical community.

CURE Celebrates 40 Years at the Forefront of GI Research

From the time of its establishment 40 years ago, the Center for Ulcer Education and Research: Digestive Diseases Research Center (CURE: DDRC) has been a nationally and internationally recognized leader in many areas of digestive diseases-related research, supporting the work of young and established investigators alike at both UCLA and the Veterans Affairs Greater Los Angeles Healthcare System-West Los Angeles (VAGLAHS-WLA). In those 40 years, though, the focus of CURE has changed dramatically, in part because the center was instrumental in solving the once-sizable public health burden of gastric ulcer — the clinical problem CURE was originally established to tackle.

"CURE has undergone a great evolution from its initial focus on ulcer to become a much more diversified and all-encompassing center," says CURE: DDRC director Enrique Rozengurt, DVM, PhD, Distinguished Professor and Ronald Hirshberg Chair in Pancreatic Cancer Research. "This is a multifaceted center that, in spite of the time that has passed, continues to be at the forefront of many advances in the digestive diseases field."

This year, the CURE center grant was renewed for yet another five-year cycle by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH). It is among the longest continuously funded digestive diseases research centers, supporting approximately 100 members and associate members. By the end of the new funding cycle, CURE: DDRC will be closing in on a half-century of continuous federal support.

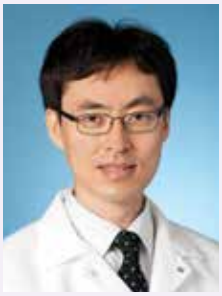
The Early Years: A Singular Focus

Founded as the Center for Ulcer Research and Education, CURE began at VA/UCLA in 1974 with an NIH program grant under the leadership of Morton I. Grossman, MD, PhD, considered the father of modern gastrointestinal endocrine physiology. At a time before effective anti-secretory therapy had been established as a treatment, peptic ulcer was a disease with high morbidity. CURE was funded for the sole purpose of finding the causes and best methods for prevention, diagnosis, and treatment of peptic ulcer and related mucosal diseases, as well as to disseminate this information to health professionals and to the public.

In CURE's first decade-plus, these goals were largely achieved. "The discoveries by CURE investigators of the mechanisms regulating gastric acid secretion

Continued on page 6

Discovery of Genetic Factors Involved in Pediatric IBD Could Pave the Way for New Treatment



Sang Hoon Rhee, PhD
Adjunct Associate Professor
Division of Digestive Diseases
David Geffen School of Medicine at UCLA

Harry Pothoulakis, MD
Professor of Medicine, Pathology and Laboratory Medicine
Eli and Edythe Broad Chair in Medicine
Director of Research, UCLA Center for Inflammatory Bowel Diseases
Chief for Research Integration, Division of Digestive Diseases

Research findings by members of the UCLA Division of Digestive Diseases and their colleagues at Pusan National University in South Korea could pave the way for new strategies in the prevention and treatment of early-onset ulcerative colitis.

Publishing in the peer-reviewed journal *Gastroenterology*, the researchers identified a combination of genetic factors – mutations in the genes interleukin-10 (IL-10) and phosphatase and tensin homologue (PTEN) – that appear to work together to cause many cases of pediatric ulcerative colitis, a severe type of inflammatory bowel disease (IBD). They also created a first-of-its-kind animal model that mimics early-onset ulcerative colitis and can now be used to test new drug candidates to treat the disease.

Approximately one in four IBD cases develop in children, including cases of ulcerative colitis that start as young as infancy or early childhood. Individuals with early-onset ulcerative colitis are at a higher risk of developing colon cancer. They are also more susceptible to liver damage because the inflammation caused by the disease results in a narrowing of the bile ducts that connect to the liver.

"We hope that identifying these key genetic factors and providing a unique research model will help lead to new approaches to treat early-onset ulcerative colitis, a devastating disease that currently has no cure," says Sang Hoon Rhee, PhD, the study's senior author and an associate adjunct professor in the Division.

Previous studies had shown that the activity of the powerful anti-inflammatory protein IL-10 is diminished in people with pediatric ulcerative colitis, but it was recognized that a non-functional IL-10 gene alone wasn't sufficient to explain early onset of the disease.

Members of Dr. Rhee's group suspected that an additional genetic factor was involved. "We knew that interleukin-10 played a role," explains Dr. Eunok Im, an assistant professor at Pusan National University's School of Pharmacy and the study's first author. "But recent clinical and experimental evidence indicated that in addition to this protein's crippled action, there may be other genetic factors at work causing early onset of this disease."

The researchers targeted the PTEN gene, which produces a protein that plays a key role in cell functions such as growth and communication. "No one thought that PTEN was associated with IBD," Dr. Rhee says. "But we hypothesized that it might have something to do with the pathogenesis because the intestinal epithelial cell needs to be readily proliferated to maintain the integrity of the intestine, and the key factor controlling this cell proliferation is the PTEN gene."

Sure enough, Dr. Rhee and colleagues found in their laboratory studies that when the PTEN gene is mutated to render it non-functional, it works in tandem with the IL-10 deficiency to cause early-onset ulcerative colitis.

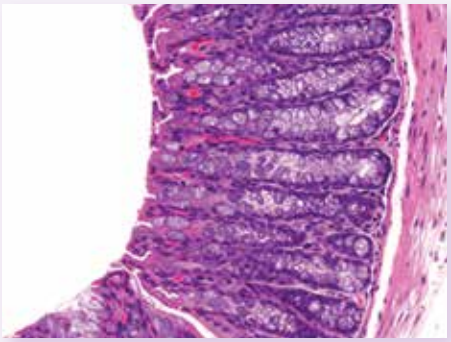
Dr. Rhee believes that the most important implication emerging from the research may be the development of a new animal model. "There had been no relevant animal model for pediatric IBD," he says. The results of his team's experiments in mice point to an invaluable new tool for testing novel prevention and treatment strategies addressing the inflammation generated by early-onset ulcerative colitis, he notes.

Among mice in the study that were deficient in IL-10, the additional loss of PTEN gene expression in the intestine caused extensive inflammation, severe colitis and early colon cancer development – as early as one month after birth. Moreover, the mice developed the symptoms and early-onset disease in much the same way that humans do. "We believe our model can be used as a test bed for drug candidates," Dr. Rhee says. "And if a small molecule can be found to regulate PTEN enzyme activity, it has the potential to be used as a therapeutic agent for pediatric IBD."

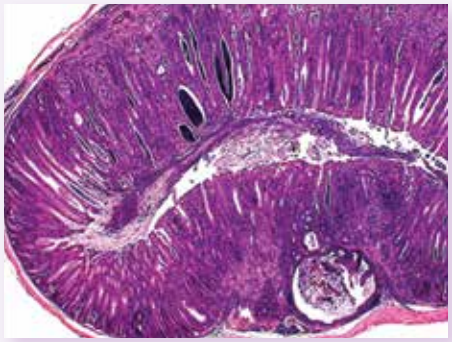
The team further found that the loss of PTEN in the intestine disrupted antibacterial activity and altered the colon's bacterial diversity. There was a large increase in a specific group of bacteria called Bacteroides, which have the ability to trigger massive inflammatory responses that cause various inflammatory diseases. Using both genetic and pharmacological interventions, the researchers inhibited the Bacteroides' ability to trigger the inflammatory responses – and in doing so, greatly reduced the occurrence of early-onset ulcerative colitis in the mice. Dr. Rhee explains that this could prove valuable in pointing the way toward new approaches to treating or preventing ulcerative colitis in humans.

More immediately, the research may have prognostic value. As a follow-up to their laboratory studies, Dr. Rhee and colleagues found that in pediatric IBD patients, PTEN gene expression is dramatically diminished. "That suggests we may be able to use PTEN as a biomarker to predict the probability of IBD disease development in children," Dr. Rhee says.

Following up on their finding that non-functional PTEN changes the microflora of the mouse intestine – affecting the pathogenesis of IBD – the research team now hopes to demonstrate the specific bacteria associated with colitis development. "Future study may help us better understand how this bacteria has the potential to elicit inflammation in the colon and explore the molecular mechanisms of how the bacteria impacts disease onset," says Dr. Charalabos "Harry" Pothoulakis, MD, professor in the Division and research director of the UCLA Center for Inflammatory Bowel Diseases, who was a co-investigator on the study along with Drs. Rhee, Im, and Jane Jung, a researcher in the Division.



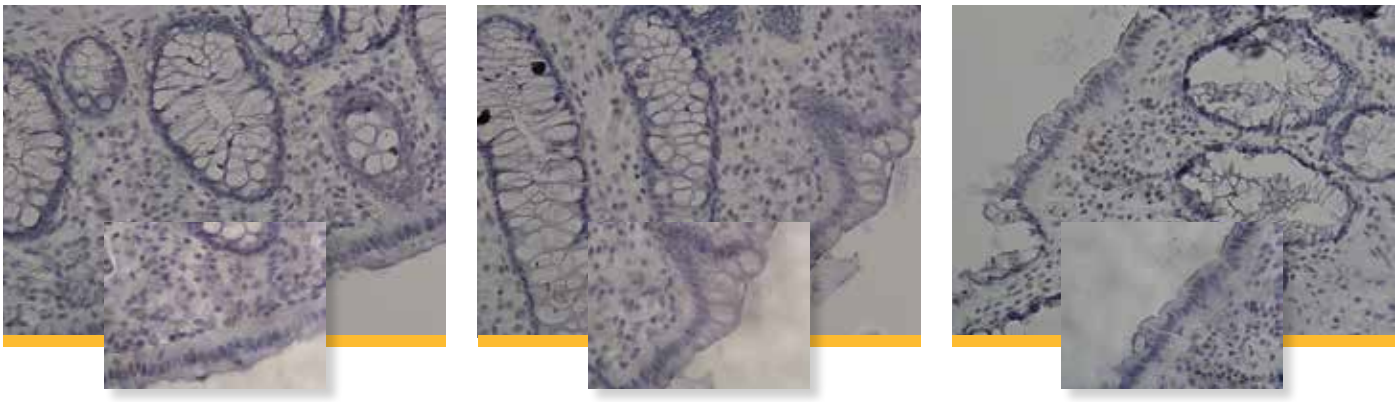
Normal



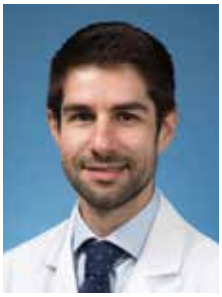
Colitis

INACTIVE UC

Phospho-STAT3 (Tyr705) (BROWN STAIN)



Loss of Non-coding RNA Associated with Pediatric IBD; Evidence of Epigenetic Regulation Points to New Research Approach



Georgios Koukos, PhD
Leader for Pediatric IBD Program
UCLA Center for Systems Biomedicine
Research Associate
Division of Digestive Diseases
David Geffen School of Medicine
at UCLA

Christos Polytarchou, PhD
Leader for IBD Program
UCLA Center for Systems Biomedicine
Assistant Professor of Medicine
Division of Digestive Diseases
David Geffen School of Medicine
at UCLA

A UCLA Division of Digestive Diseases research group, taking a novel approach to studying inflammatory bowel disease (IBD) in children, has found that the loss of a specific non-coding RNA, also known as a microRNA (miR), may play a key role in ulcerative colitis (UC) in children.

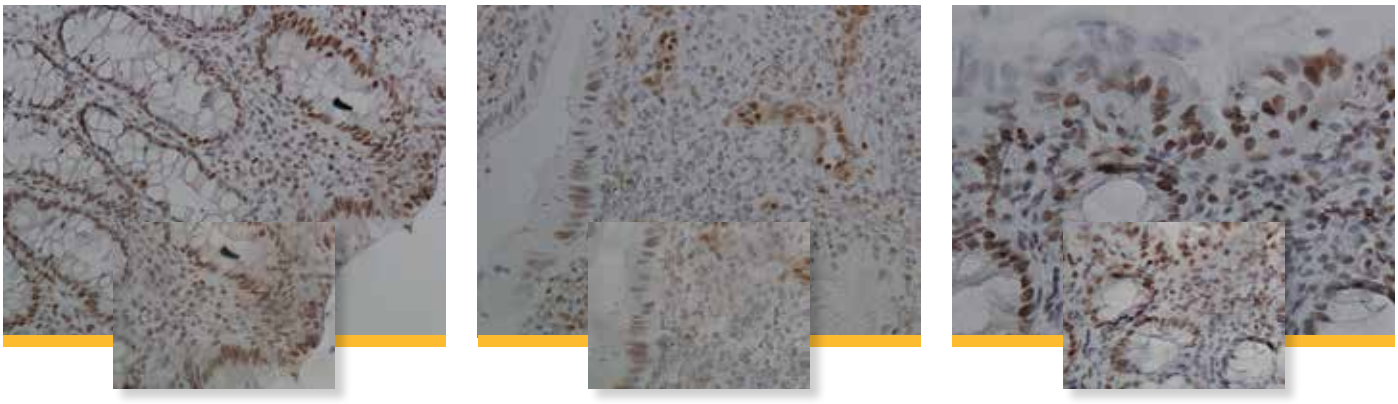
Reporting in the October 2014 issue of the journal *Gastroenterology*, the researchers identified several miRs that in human colonocytes serve as potent regulators of IL6-STAT3, an inflammatory pathway known to play a key role in IBD. They found that one of these, miR-124, is deregulated specifically in pediatric patients with active UC, leading to increased levels of STAT3 expression. Equally significant, the research team discovered that the miR-124/STAT3 pathway is epigenetically regulated via hypermethylation of the promoter region of the gene that encodes miR-124 – suggesting an important new way of studying IBD, as well as the potential for new therapeutic strategies.

The complex nature of the chronic IBDs ulcerative colitis and Crohn's disease has made it difficult to pinpoint their causes, notes Georgios Koukos, PhD, leader of the pediatric IBD program at the Center for Systems Biomedicine within the Division, who headed the study. "These are multifactorial diseases," Dr. Koukos explains. "For many years, research has focused on finding specific genes or networks, but none have been found to contribute in a major way."

Dr. Koukos and colleagues took a different approach by investigating the role of miRs in regulating IL6-STAT3, and then examining the importance of these regulatory processes in tissue samples from patients. MicroRNAs are small, non-coding RNA oligonu-cleotides that can regulate the expression of a large number of genes and have been implicated in various human diseases. Although several miRs have been associated with IBD, their roles and functions have yet to be described. STAT3, the receptor for the IL6 gene, is known to be upregulated in adult UC patients, but it has not been clear how this pathway becomes activated.

ACTIVE UC

Phospho-STAT3 (Tyr705) (BROWN STAIN)



The researchers specifically addressed the question in the context of pediatric UC because fewer environmental factors are involved in IBD for children than for adults, making it easier to study the genetic factors involved in the disease process. In nearly 25 percent of patients, IBD presents by the age of 20. The disease is typically more severe in these early-onset cases than in adult-onset IBD.

The UCLA researchers screened 316 miRs to determine which were able to regulate the IL6-STAT3 pathway in vitro. They found five that appeared to play an important role in downregulating STAT3 activation. In subsequent studies of colon tissue samples from children with active UC, one of those, miR-124, was observed to be the most potent: Lower levels of miR-124 led to higher levels of STAT, producing the activated inflammatory response. A similar inverse association was found in mice. Importantly, the suppression of miR-124 was observed only in pediatric IBD patients and not in adults, suggesting that a different mechanism is involved in the development and regulation of this disease in children.

Next, Dr. Koukos and colleagues investigated how miR-124 expression is downregulated. They found that the promoter region of the gene encoding miR-124 is hypermethylated in pediatric UC patient tissues, resulting in the downregulation of its expression. "Methylation is an epigenetic mechanism controlling gene regulation," Dr. Koukos explains. "It's not a mutation that occurs in the gene, which is what the traditional focus has been, but it affects gene expression."

The knowledge that methylation is causing the downregulation suggests the possibility that demethylating agents, which are increasingly being used for cancer treatment, could have therapeutic potential in IBD as a way of increasing miR-124 expression. "Our findings provide a new target specific to pediatric UC," says Dr. Koukos. "Perturbations of the epigenetically regulated miR-124/STAT3 pathway may lead to novel therapeutic approaches with great impact in pediatric UC, as well as other inflammatory diseases where this regulatory mechanism may play an important role."

"Ours and other studies have shown that microRNA mimics or microRNA inhibitors have therapeutic potential in different types of cancer and autoimmune diseases," adds Christos Polytarchou, PhD, a member of the study team. "Importantly, miR inhibitors are already in clinical trials. We have developed in animals an experimental therapeutic protocol for the intra-colonic administration of chemically modified oligonucleotides. Administration of an miR-124 mimic, as enema, may hold promise as a therapeutic approach for pediatric IBD patients."

In addition, Dr. Koukos notes, the discovery of a notable decrease of miR-124 in pediatric UC colon tissue samples make it a potential candidate as a biomarker for active pediatric UC — used both as a marker for disease activity to monitor the effects of therapeutic efforts, as well as for diagnostic purposes.

These findings are just the beginning. On the heels of their study, Dr. Koukos and colleagues have conducted further investigations looking at other miRs that may be implicated in the disease. They have identified new targets — miRs involved in other pathways that play a role in IBD beyond the inflammatory processes.

"What's most important is that we have provided the first evidence for an epigenetic regulatory mechanism in pediatric IBD," Dr. Koukos says. "This appears to have been an underestimated aspect of the disease, and it opens the door for studying other regulating genes that might have been overlooked in the past."

CURE Continued from page 1

were instrumental to the development of the major drugs that have provided effective treatment and the cure of peptide ulcer disease," says Catia Sternini, MD, professor in the UCLA Division of Digestive Diseases and director of the CURE: DDRC Pilot and Feasibility Studies Program, which supports young investigators through seed funding.

Much of the progress had to do with the development of H2 antagonists that fundamentally changed the concepts surrounding the stimulation of parietal-cell acid secretion. Initially, much of CURE's research involved determining the pathways responsible for parietal-cell stimulation. After CURE established the mechanism of acid secretion as being a function of gastric parietal-cell H, K-ATPase, a new era in ulcer therapy began with the introduction of benzimidazoles.

George Sachs, MD, DSc, recruited as CURE director a year after the death of Dr. Grossman in 1981, headed breakthrough studies on proton-pump inhibitors, leading to the start of a new therapeutic strategy involving the suppression of acid leading to the remission of the ulcer formations exacerbated by the acid. "Dr. Sachs, by contributing to the understanding of the proton pump at the cellular level and targeting it with a drug, completely revolutionized the treatment of gastric ulcer," says Yvette Taché, PhD, a professor in the UCLA Division of Digestive Diseases who has been a member of CURE since 1982 and serves as associate director. Dr. Sachs and John Walsh, MD, who was CURE Director from 1987 until his untimely death in 2000, later developed methods to study intracellular Ca2+ responses to various peptides in gastric G and D cells, and to define inhibitory receptors on isolated ECL cells that oppose the stimulatory actions of gastrin. This led to prominent anti-acid clinical trials led by Dr. Walsh of histamine antagonists that served as the earlier generation of the anti-secretory drugs used today. Dr. Walsh also made the important finding that gastrin, a critical regulator of acid gastric secretion, stimulates mucosal growth, which marked the beginning of a new era at CURE focusing on long-term effects of gastrointestinal peptides.

Evolution as a Research Center

CURE received funding in 1989 to become an NIH/NIDDK research core center and began to delve more deeply into understanding the molecular and cellular mechanisms of other conditions underlying normal and abnormal processes of the digestive system, from inflammatory diseases and cancer to brain-gut interactions and functional disorders.

Among the most renowned was work that initially started at CURE in the early 1980s around understanding neural pathways and the brain-gut axis. "It became very clear that the brain-gut axis was playing a major role in the development and exacerbation of irritable bowel syndrome," says Dr. Taché. Along with the work of Emeran A. Mayer, MD, PhD, a professor in the Division, co-director of CURE and director of the Gail and Gerald Oppenheimer Family Center for Neurobiology of Stress at UCLA, Dr. Taché's studies contributed to a new understanding — Dr. Taché through laboratory findings and Dr. Mayer from the clinical standpoint — of how brain activity changes in response to visceral pain in IBS patients. Their work represents an important landmark in the field of gastrointestinal disorders opening new avenues for the diagnosis and treatment of functional disorders and setting the tone for further studies by CURE: DDRC researchers.

Dr. Rozengurt, recruited to UCLA in 1997, pioneered the elucidation of the mechanisms of action of gastrointestinal (GI) peptides, with fundamental contributions that identified novel molecular mechanisms that mediate the multiplication and movement of intestinal and pancreatic epithelial cells. Indeed, his seminal studies moved the focus of CURE from classical hormone physiology to a new understanding of the mechanism of action of gut hormones and peptides as potent growth factors. The studies opened a different field of research at CURE with important clinical implications for the prospect of developing therapeutic approaches for gastrointestinal cancers. More recently, the Center has emerged as a leader in unraveling the pathophysiology of inflammatory bowel disease under the leadership of Charalabos "Harry" Pothoulakis, MD, research director of the Division's Center for Inflammatory Bowel Diseases and an associate director of CURE, and in the identification of novel targets for therapeutic intervention in pancreatic cancer, under the leadership of Dr. Rozengurt. Dr. Pothoulakis has contributed to the understanding of the pathophysiology of gastrointestinal diseases with his discovery that neuropeptides act as mediators of intestinal inflammation in *Clostridium difficile* toxin-induced diarrhea and inflammatory bowel disease. As CURE researchers continue to learn more about

cell signaling and inflammatory responses in both the pancreas and the intestine, new efforts are also being directed toward stem cell research as it pertains to the intestine. The current programs supported by CURE can be broadly divided into three areas: the molecular and integrative mechanisms of gastrointestinal and pancreatic physiology and inflammation; bidirectional brain-gut interactions and functional disorders of the digestive system; and the mechanism of action of neuro-hormonal GI signals: receptor regulation, signal transduction, and control of normal and abnormal cell proliferation.

"The research at CURE has had and continues to have a major impact in digestive diseases by providing essential knowledge of how the digestive system works, elucidating the mechanisms underlying different pathological conditions, advancing the diagnostic abilities for digestive diseases and translating the fundamental knowledge of function and diseases of the digestive system in the development of targeted therapies," says Dr. Sternini.

An Infrastructure for Growth, Efficiency and Exchange of Ideas

The creation of the CURE: DDRC in 1989 provided a comprehensive mechanism of programmatic integration to support, stimulate and enhance digestive diseases-related research at UCLA and the VAGLAHS-WLA — setting up an infrastructure that helped to accelerate the research, recruitment, training and continued development of young investigators, as well as providing a forum for faculty to advance the understanding of fundamental mechanisms relating to the function and diseases of the digestive system through synergistic efforts across disciplinary boundaries. "CURE has become much more multidisciplinary and interdepartmental," Dr. Rozengurt explains. "Obviously, the Division of Digestive Diseases is the focal point, but we have members and collaborations all over UCLA, which is essential for tackling complex problems."

One of the key ways in which CURE supports digestive diseases programs at UCLA is through its Biomedical Research Cores, which give members easy access to essential technologies and clinical materials, as well as specialized expertise needed to carry out experiments. Among other things, these cores provide access to modern cellular imaging to study signaling proteins and their functions, intestinal stem cell biology approaches, animal models and techniques for studying integrative physiology and pathophysiology, molecular vectors to express a wide variety of proteins, and a broad range of techniques and patients for clinical studies.

Through the Pilot and Feasibility Study program headed by Dr. Sternini, CURE is able to support the development of new programs and ideas in digestive diseases-related research — providing the seed grants so critical for investigators looking to test a promising idea as the basis for obtaining larger funding. The program is particularly important in developing the careers of junior faculty. Junior and senior faculty alike also benefit from CURE's seminar program, which brings scientists together to present research, exchange ideas and foster collaborations. An annual full-day scientific meeting combines formal lectures with a poster session and discussions (see page 8 for 2015 meeting information).

Keys to Success

All of these components combine to make CURE a center where investigators have been uniquely able to translate fundamental advances in molecular, cellular and integrative physiology into studies that have reaped therapeutic benefits. "With the blend of basic scientists and clinical investigators along with all of the basic and clinical cores, CURE has always excelled at moving research from the bench to the bedside," says Dr. Taché.

Beyond the strong infrastructure, CURE has succeeded on the basis of its leaders, who in turn have brought other top researchers into the fold. It started with the founder and first director, Dr. Grossman, who in addition to his pioneering work set the tone for CURE with his energy, dedication and integrity. Dr. Grossman's most important scientific contributions lay in defining the secretory mechanisms of the stomach and pancreas as well as the actions of regulatory gastrointestinal peptides.

Dr. Grossman was later joined by Charles F. Code, MD, PhD, a renowned gastrointestinal physiologist, who served as associate director. Dr. Sachs took the leadership reins in 1982; he served as co-director after Dr. Walsh was appointed director in 1987, with Dr. Taché and Dennis M. Jensen, MD, serving as associate directors. Drs. Mayer, Rozengurt and Ernest Wright, DSc, FRS, were added to the team as associate directors in 1998 to reflect the new directions in enteric neuroscience, signal transduction, and molecular transport.

Continued on page 8

Following Dr. Walsh's death in 2000, Dr. Rozengurt was appointed director. "From the beginning, Dr. Grossman attracted talented young investigators from all over the world, and CURE became a mecca for training related to gastric ulcer and endocrinology of the gut," says Dr. Taché. "That tradition continued, and with all the trainees going on to become leaders in the gastroenterology field across the nation and around the world after getting their start here, the center continued to have great visibility and a reputation for impact."

For Dr. Sternini, CURE's long-standing success lies not only in its people, but also its ability to adapt to the changing needs of the field. "Behind the continued success and tremendous achievements of CURE throughout the years is the willingness of CURE investigators to reinvent themselves," she says. "By expanding interests and using cutting-edge technologies, CURE has always remained at the forefront in many areas of digestive diseases-related research."

2015 CURE Annual Research Meeting and Poster Session

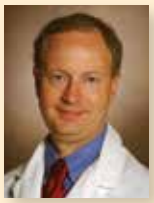
CURE: Digestive Diseases Research Center

March 12, 2015

UCLA Sunset Village on the Campus of UCLA
Non-CME Program

Course Director

Enrique Rozengurt, DVM, PhD
Distinguished Professor of Medicine
Hirschberg Memorial Chair in Pancreatic Cancer Research
Director, CURE: Digestive Diseases Research Center
David Geffen School of Medicine at UCLA



Invited John H. Walsh Memorial Lecturer

Richard Peek, MD
Director, Division of Gastroenterology, Hepatology and Nutrition
Professor of Medicine and Cancer Biology
Vanderbilt University

Meeting Information

Meeting Location

UCLA Sunset Village on the Campus of UCLA
Northwest Campus Auditorium in Covel Commons
330 DeNeve Drive, Los Angeles, CA 90024

Overnight Accommodations

CURE attendees have access to the room block for the Mellinkoff Symposium.
See page 10 for details.

Registration Fee

$100 – Non-UCLA Physicians

Complimentary – UCLA Physicians, Fellows and Residents

Symposium Inquiries and Registration

Contact Jacqueline Ismen at **jismen@mednet.ucla.edu**
or call **(310) 312-9284.**

Course Agenda

8:00 am	Breakfast and Registration
8:25 am	**Welcoming Remarks and Conference Overview**
8:30 am	Topics in Basic and Translational Science
	The Cell Biology of Pancreatic Cell Inflammation *Anna Gukovskaya, PhD, UCLA*
	Intestinal and Colonic Stem Cells *Martín G. Martín, MD, UCLA*
	The Role of Neuropeptides in Homeostasis and Inflammation in the GI Tract *Harry Pothoulakis, MD, UCLA*
	Taste Receptor Expression and Function in the GI Tract *Catia Sternini, MD, AGAF, UCLA*
	The Impact of Stress on GI Functions *Yvette Taché, PhD, UCLA*
12:00 pm	**Lunch**
1:15 pm	Remarks *A. Eugene Washington, MD* *Vice Chancellor, Health Sciences* *Dean, David Geffen School of Medicine at UCLA*
1:30 pm	State of CURE *Enrique Rozengurt, DVM, PhD*
2:00 pm	John H. Walsh Memorial Lecturer
	Gastric Inflammation, *H. Pylori* and Cancer *Richard Peek, MD, Vanderbilt University*
3:00 pm	Basic, Translational and Clinical Science Poster Session
5:00 pm	**Adjourn**

UCLA Course Faculty

Anna Gukovskaya, PhD +
Professor-in-Residence
Department of Medicine
Director, Pancreatic Research Group
UCLA/VA Greater Los Angeles Healthcare System
Senior Research Career Scientist
VA Medical Research

Martín G. Martín, MD, MPP +
Professor of Pediatric Gastroenterology and Nutrition
Director of the UCLA Pediatric Diarrheal Center
Pediatric Department Associate
Vice Chair of Translational Research

Harry Pothoulakis, MD * +
Professor of Medicine, Pathology and Laboratory Medicine
Eli and Edythe Broad Chair in Medicine
Director of Research, UCLA Center for Inflammatory Bowel Diseases
Chief for Research Integration, Division of Digestive Diseases

Catia Sternini, MD, AGAF * +
Professor of Medicine and Neurobiology
Associate Director, CURE: Digestive Diseases Research Center
Core Director, Imaging and Signaling Cell Biology
Director, Pilot and Feasibility Studies Program

Yvette Taché, PhD * +
Professor of Medicine
Director, CURE: Digestive Diseases Research Center, Animal Core
Co-Director, Center for Neurobiology of Stress & Women's Health
VA Greater Los Angeles Healthcare System

* Division of Digestive Diseases
\+ David Geffen School of Medicine

Accreditation

The Office of Continuing Medical Education, David Geffen School of Medicine at UCLA is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The Office of Continuing Medical Education, David Geffen School of Medicine at UCLA designates this live activity for a maximum of 16.5 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

IN RECOGNITION OF DR. SHERMAN M. MELLINKOFF'S COMMITMENT TO MEDICAL EDUCATION AND RESEARCH

3rd Annual UCLA-Mellinkoff Gastroenterology and Hepatology Symposium

A Case-oriented Approach to Common and Difficult Issues in the Practice of Gastroenterology

March 13 – 15, 2015 • Beverly Hilton, Beverly Hills, CA
To register, go to: cme.ucla.edu/courses

16.5 AMA PRA Category 1 Credits™
Up to 19.5 Contact Hours (19.5 are ABCGN GI-specific Contact Hours)
$350 / $250 / $50 Registration
Complimentary Hands-on Session* / Limited to 30 Physicians / Non-CME

Course Directors

Eric Esrailian, MD, MPH
Co-Chief, Division of Digestive Diseases
Lincy Foundation Chair in Clinical Gastroenterology
Associate Clinical Professor of Medicine

V. Raman Muthusamy, MD
Director, Interventional Endoscopy
Associate Director, Endoscopy
Clinical Professor of Medicine

Bennett Roth, MD
Chief, Gastrointestinal Endoscopy
Director, Medical Procedure Units
Director, Post-Graduate Education Programs
Professor of Clinical Medicine

The 3rd Annual UCLA-Mellinkoff Gastroenterology and Hepatology Symposium

will be centered upon a series of directed lectures and illustrative cases devoted to providing a roadmap and understanding of the most up-to-date means by which to address perplexing management decisions for our patients. The agenda has been specifically designed to offer practical approaches that healthcare professionals may readily integrate into their daily practice.

Overnight Accommodations

A limited block of rooms, at a special rate of $269 (deluxe) or $309 (studio suite) + tax, has been reserved at the Beverly Hilton. This special room block expires January 30, 2015. Please call (310) 274-7777 and ask for the "UCLA Division of Digestive Diseases" block. Or make a reservation online at: **www.beverlyhills.hilton.com/UCLAMellinkoffSymposium2015**

For more information about the hotel, visit **www.beverlyhilton.com**

CME OFFICE OF CONTINUING MEDICAL EDUCATION
DAVID GEFFEN SCHOOL OF MEDICINE at UCLA

Agenda

Friday, March 13

7:00 am Registration and Breakfast

7:50 am Welcoming Remarks
Gary Gitnick, MD, UCLA

7:55 am Course Overview
V. Raman Muthusamy, MD, UCLA &
Bennett E. Roth, MD, UCLA

Colorectal Issues Moderator:
Lynn Shapiro Connolly, MD, MSCR, UCLA

8:00 am Multi-target Stool DNA Test (Cologuard) – A New High Bar for Non-invasive Colorectal Cancer Screening
David A. Ahlquist, MD
Mayo Clinic, Rochester

8:25 am Pitfalls and Needs in Preparing for Colonoscopy
Jeffrey R. Lewis, MD, UCLA

8:50 am Defecation Disorders: Constipation and Incontinence – Diagnostic and Therapeutic Options
Lin Chang, MD, UCLA

9:15 am Q & A
Panel

9:35 am Case Presentations
Lead: *Lynn Shapiro Connolly, MD, MSCR, UCLA*
Panel

10:35 am Break

Pancreatico-biliary Disorders
Moderator: V. Raman Muthusamy, MD, UCLA

10:55 am Pancreatic Cysts: Resect, Watch or Ignore
James M. Scheiman, MD
University of Michigan

11:20 am Recurrent Acute Pancreatitis: Evaluation and Management
Alireza Sedarat, MD, UCLA

11:45 am Sphincter of Oddi Dysfunction: Fact or Fiction
Rabindra R. Watson, MD, UCLA

12:10 pm Q & A
Panel

12:30 pm Lunch

Pancreatico-biliary Disorders (Continued)
Moderator: V. Raman Muthusamy, MD, UCLA

1:30 pm Case Presentations
Lead: Stephen Kim, MD, UCLA
Panel

2:30 pm Break

GI Emergencies
Moderator: Mark Ovsiowitz, MD, UCLA

2:50 pm Managing GI Bleeding
Dennis M. Jensen, MD, UCLA

3:15 pm Foreign Bodies
Thomas Kovacs, MD, UCLA

3:40 pm Managing Endoscopic Complications
Rabindra R. Watson, MD, UCLA

4:05 pm Q & A
Panel

4:25 pm Case Presentations
Lead: Mark Ovsiowitz, MD, UCLA
Panel

5:25 pm Adjourn

Saturday, March 14

7:00 am Breakfast

7:55 am Welcoming Remarks
V. Raman Muthusamy, MD, UCLA

Inflammatory Bowel Diseases
Moderator: Daniel Hommes, MD, PhD, UCLA

8:00 am Therapeutic Monitoring in IBD: A Clinician's Perspective on Use of Serologies, Bio-markers and Levels in Practice
David T. Rubin, MD
The University of Chicago

8:25 am Babies, Breastfeeding and Beyond: Update on IBD and Pregnancy
Jennifer M. Choi, MD, UCLA

8:50 am Risk of IBD Therapy: Infections, Malignancy and Prevention
Christina Ha, MD, UCLA

9:15 am Q & A
Panel

9:35 am Case Presentations
Leads: Jennifer M. Choi, MD, UCLA
and Christina Ha, MD, UCLA
Panel

10:35 am Break

Issues of the Foregut
Moderator: Kevin Ghassemi, MD, UCLA

10:55 am Atypical and Extra-esophageal Issues in GERD: Get That ENT Guy Off My Back
Michael F. Vaezi, MD, PhD
Vanderbilt University Medical Center

11:20 am Managing Motility Disorders of the Foregut: Achalasia
Jeffrey L. Conklin, MD, UCLA

11:45 am Managing Motility Disorders of the Foregut: Gastroparesis
Bennett E. Roth, MD, UCLA

12:10 pm Controversies in Barrett's Esophagus: Whom to Screen, When to Ablate, How to Follow
V. Raman Muthusamy, MD, UCLA

12:35 pm Q & A
Panel

12:55 pm Lunch

Issues of the Foregut (Continued)
Moderator: Kevin Ghassemi, MD, UCLA

1:55 pm Case Presentations
Lead: Kevin Ghassemi, MD, UCLA
Panel

2:55 pm Adjourn – Didactic

Sunday, March 15

7:55 am Welcoming Remarks
Eric Esrailian, MD, MPH, UCLA

Liver Disease
Moderator: Mohamed El Kabany, MD, UCLA

8:00 am Viral Hepatitis: A New Dawn of Therapy
Sammy Saab, MD, MPH, UCLA

8:25 am Your Liver is Full of Fat: What Should/ Can You Do?
Simon W. Beaven, MD, PhD, UCLA

8:50 am Decompensated Liver Disease: Too Late to Help?
Bruce A. Runyon, MD, UCLA

9:15 am Auto-immune Hepatic and Biliary Disorders
Steven-Huy Han, MD, UCLA

9:40 am Break

10:00 am Q & A
Panel

10:20 am Case Presentations
Lead: Francisco Durazo, MD, UCLA

11:20 am Adjourn – Boxed Lunch

*Complimentary Hands-on Session – Saturday, March 14

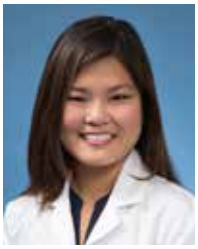
The hands-on session will provide a valuable learning opportunity, though no CME credit will be issued to participants. The hands-on session is limited in its number of participants. Separate registration is required on a first-come, first-served basis.

3:00 - 6:00 pm Hands-on Session – Physicians Only
Faculty: *Drs. Kevin Ghassemi, Stephen Kim, Thomas Kovacs, V. Raman Muthusamy, Mark Ovsiowitz, Bennett E. Roth, James M. Scheiman, Alireza Sedarat and Rabindra R. Watson*

UCLA Division of Digestive Diseases Welcomes Eight New Faculty Members

Sittiporn Bencharit, MD | Assistant Clinical Professor of Medicine

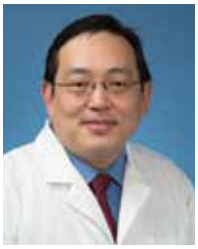
Dr. Sittiporn Bencharit has been practicing in Santa Clarita since 1988. Born in Bangkok, Thailand, he attended boarding school in Hong Kong and then attended the University of Wisconsin Stevens Point for his undergraduate education. He graduated from Yale University School of Medicine in 1980, and after obtaining his residency training in internal medicine at Northwestern Memorial Hospital, he practiced primary care in rural Indiana for three years. Dr. Bencharit completed his fellowship training in gastroenterology at the University of California, San Diego in 1988. He is board-certified in internal medicine and gastroenterology.



Maggie Ham, MD | Clinical Professor of Medicine

Dr. Maggie Ham practices general gastroenterology with interests in women's health, inflammatory bowel disease, peptic ulcer disease, celiac disease, irritable bowel syndrome, gastroesophageal reflux disease, colorectal cancer screening, fecal incontinence, and liver disease. Her research interests have included peptic ulcer disease, mucosal defense, and inflammatory bowel disease. She has had several peer-reviewed publications and is board-certified in internal medicine and gastroenterology.

Dr. Ham graduated in 2007 from the David Geffen School of Medicine at UCLA, where she was elected to Alpha Omega Alpha and awarded the Emil Bogen Research prize. She completed her residency in internal medicine at UCLA, followed by her gastroenterology fellowship at Beth Israel Deaconess Medical Center, a teaching hospital of Harvard Medical School. During that time, Dr. Ham was awarded the Fellowship2Leadership grant supported by Salix Pharmaceuticals, and the Inflammatory Bowel Disease Working Group research grant.



Michael C. Jean, MD | Assistant Clinical Professor of Medicine

Dr. Michael C. Jean practices general gastroenterology, with particular interests in colon cancer screening, gastrointestinal bleeding, gastroesophageal reflux, dysphagia, inflammatory bowel disease, and irritable bowel syndrome, as well as liver disease and hepatobiliary diseases. He is board-certified in gastroenterology. Dr. Jean completed a combined BA/MD program at Lehigh University and the Medical College of Pennsylvania. He completed his internal medicine residency at Evanston Northwestern Hospital, then went on to complete his gastroenterology fellowship at the Medical College of Wisconsin.

Rajinder Kaushal, MD | Assistant Clinical Professor of Medicine

Dr. Rajinder Kaushal specializes in therapeutic endoscopy and ERCP, performing difficult colonoscopy and polypectomy, gastrointestinal infections, fecal microbiota transplant for refractory or recurrent *C. difficile* infection, and total parenteral nutrition. Prior to joining UCLA, he was in private practice in Santa Clarita. He has served as chairman of medicine, medical director of the GI Lab and member of the Medical Executive Committee and Board of Directors at Henry Mayo Newhall Hospital in Valencia, Calif.

After obtaining his medical degree in India, Dr. Kaushal received further medical education in England, specializing in infectious disease and tropical medicine. Certified by the School of Tropical Medicine and Hygiene at the University of Liverpool and the Royal Colleges of Physicians and Surgeons of Edinburgh and Glasgow, Scotland, he helped to establish one of the world's first isolation units in Liverpool for treatment of highly infectious diseases such as Ebola and Lassa fever. He completed his internal medicine residency at Mount Sinai School of Medicine/City Hospital Center in Elmhurst, N.Y., and his gastroenterology fellowship at Wayne State University in Detroit. As a fellow, he developed a special interest in the field of therapeutic ERCP and received further training in Germany from one of the world's leading experts and pioneers of the procedure.

David E. Krieger, MD, PhD | Assistant Clinical Professor of Medicine

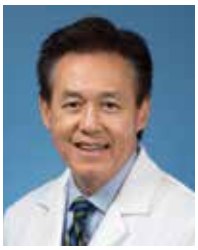
Dr. David E. Krieger practices general gastroenterology, with particular clinical interests in gastrointestinal endoscopy, colon cancer screening, gastroesophageal reflux disease, abdominal pain, ulcer disease, inflammatory bowel syndrome, hepatitis, and gallstones. Since 1984, he has practiced in the Santa Clarita Valley and Mission Hills, Calif. In 1989, Dr. Krieger developed and has since served as the medical director of one of the first freestanding Medicare-certified endoscopy centers in Southern California. Dr. Krieger is board-certified in internal medicine and gastroenterology, and was recognized as one of the "Super Doctors of Southern California" from 2010-2012.

Dr. Krieger attended The Rockefeller University, earning a PhD in Biochemistry. He graduated from Yale Medical School, followed by a residency/fellowship in internal medicine and gastroenterology at the Wadsworth VA Hospital and UCLA School of Medicine.

Hamed Nayeb-Hashemi, MD | Clinical Instructor of Medicine

Dr. Hamed Nayeb-Hashemi's interests include liver diseases, medical education, reflux disease, peptic ulcer disease, fecal incontinence and perianal complaints, irritable bowel syndrome, inflammatory bowel disease, colorectal cancer screening, and celiac disease. He is a member of American Gastroenterological Association Academy of Educators and is board-certified in internal medicine.

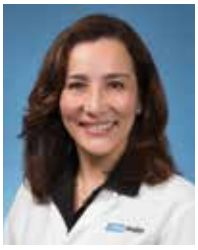
Dr. Nayeb-Hashemi graduated from Northeastern University before attending the University of Pittsburgh School of Medicine, from which he received his MD in 2007. He completed both his internship and residency in internal medicine at Ronald Reagan UCLA Medical Center. He then completed his fellowship training in gastroenterology at Brigham and Women's Hospital/Harvard Medical School. During that time, he was active in researching liver diseases and liver cancer. In the final year of his fellowship, he was named the Brigham and Women's Hospital Teaching Fellow in Gastroenterology, in addition to being recognized for excellence in tutoring by Harvard Medical School.



Michael G. Quon, MD | Assistant Clinical Professor of Medicine

Dr. Michael G. Quon joined the Division faculty as part of UCLA Health Santa Clarita Digestive Diseases after spending the past 22 years in private practice with the Santa Clarita Gastroenterology Medical Group. He practices general gastroenterology and liver diseases, with particular interests in colon cancer screening, hemorrhoidal banding, pancreatic diseases, viral hepatitis, irritable bowel syndrome and inflammatory bowel disease. Dr. Quon is board-certified in internal medicine and gastroenterology.

Dr. Quon earned his Bachelor of Science degree in biological sciences from the University of Southern California, graduating summa cum laude. He received his medical degree from the Keck School of Medicine at USC and completed his internship and residency in internal medicine at LAC+USC Medical Center, where he subsequently completed his three-year gastroenterology fellowship training, including a year dedicated to bench research in pancreatic diseases.



Claudia Sanmiguel, MD | Clinical Instructor of Medicine

Dr. Claudia Sanmiguel has joined the Division faculty as program director of the Ingestive Behavior and Obesity Program, where she is conducting research on brain-gut interactions with an emphasis on the role of the brain in the development of obesity. Dr. Sanmiguel's clinical expertise is in gastrointestinal motility disorders, including achalasia, spastic disorders of the esophagus, gastroesophageal reflux (GERD), gastroparesis and motor disorders of the colon and anorectal region. She has published original research on gastrointestinal manometry/intraluminal impedance and on the effect of electrical stimulation on GERD, gastroparesis and constipation, as well as in obesity and diabetes.

After graduating from the Pontificial Javeriana University School of Medicine in Bogota, Colombia, Dr. Sanmiguel completed her internship and residency training in internal medicine at the UCLA/Cedars-Sinai Medical Center and fellowship in gastroenterology at the UCLA Division of Digestive Diseases. She practiced gastroenterology in her native country of Colombia before moving to Canada and then the United States to pursue her interest in research on motility disorders. As part of her research training, she spent time at the University of Alberta in Edmonton, Canada, and two years at the Cleveland Clinic as a research fellow in gastrointestinal motility. She also worked as a researcher in the GI Motility Program at Cedars-Sinai Medical Center.

David Geffen School of Medicine

Division of Digestive Diseases
405 Hilgard Ave
BOX 956949, 2114 PVUB
Los Angeles, CA 90095-6949

UCLA Gastroenterology and GI Surgery Ranked No. 5 in the Nation

— *U.S. News & World Report*

UCLA DIVISION OF DIGESTIVE DISEASES

CHIEFS
Gary Gitnick, MD

Eric Esrailian, MD, MPH
eesrailian@mednet.ucla.edu

BUSINESS DEVELOPMENT
Trisha James, MBA
trishajames@mednet.ucla.edu

DEVELOPMENT
Laurel Zeno
lzeno@support.ucla.edu

FINANCE AND OPERATIONS
Adriana Centeno
acenteno@mednet.ucla.edu

CONTRIBUTING WRITER
Dan Gordon

DESIGN
Oglesby Design

Go to **gastro.ucla.edu**
to learn more about the UCLA Division of Digestive Diseases.

UCLA Physician Referral Service **1-800-UCLA-MD1 (800-825-2631)**

Digestive Diseases Call Center **(310) 825-1597**

UCLA's Division of Digestive Diseases has once again been ranked in the top ten nationwide by *U.S. News & World Report.* We have maintained this ranking since 1990, when the ratings began.

The UCLA Health System's hospitals in Westwood and Santa Monica have also been named to *U.S. News & World Report's* Best Hospitals 2014-15 Honor Roll. UCLA was ranked No. 5 in the country and No. 1 in both California and the Los Angeles metropolitan area.

UCLA Health

A Report of the UCLA Digestive Diseases Division