Environmental Factors in Inflammatory Bowel Disease Pathogenesis

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The global burden of inflammatory bowel diseases (IBD) is substantial. IBD tends to be diagnosed before the age of 35. It exacts a heavy quality of life toll, affecting jobs and relationships. The cost of caring for these chronically ill patients can be prohibitive to healthcare systems. And the problem is growing. Approximately 1.6 million people in the U.S. and roughly 3.7 million in Europe have been diagnosed, while newly developed countries throughout the globe are experiencing sharp increases of their own. These increases are well beyond what one could ascribe to genetics; clearly, as we seek to unravel the mysteries involved in the pathogenesis of IBD, we must home in on the role of environmental factors.

This issue of Beyond the Scope focuses on the internationally renowned work of our faculty in identifying key environmental factors contributing to the development of IBD. Their discoveries are not only helping to unravel the mysteries driving IBD pathogenesis at the molecular and cellular levels, but they are also providing targets for new therapeutic approaches – some of which are currently under investigation. As Dr. Dimitrios Iliopoulos explains in an introduction to the theme (page 1), much of this work is focused on how the environment influences IBD pathogenesis through changes in the epigenome and microbiome. In the epigenome category, Dr. Iliopoulos and his colleagues (page 2) are leaders in the use of cutting-edge approaches such as systems science and artificial intelligence to discover the role of DNA methylation and histone modifications in the development of IBD. The group headed by Dr. Charalabos “Harry” Pothoulakis (page 4) is internationally recognized for its work in describing how microRNAs are involved, and in developing treatment strategies that capitalize on these findings. Dr. David Padua’s team (page 6) is looking at the role of long non-coding RNAs in the inflammation that is central to IBD. Our work in the microbiome realm includes a group headed by Dr. Jonathan P. Jacobs (page 8) that is investigating how the intestinal microbiome contributes to IBD development. Dr. Emeran A. Mayer and his colleagues (page 10) are conducting pioneering studies exploring the interactions between IBD and the nervous system, amid mounting interest in the role of brain alterations in IBD pathogenesis.

The IBD-related research highlighted in this issue is, of course, only part of our division’s work. In this issue we also report on the exciting new NIH-funded consortium headed by Dr. Yvette Taché (page 13) to provide the first detailed structural and functional maps of the human and pig nervous systems as they relate to the colon – work expected to pave the way for a new class of electroceutical treatments for colonic disorders. We also continue to be strongly committed to education, perpetuating the legacy of longtime division leaders such as Dr. Vay Liang W. (Bill) Go, who recently received a prestigious Lifetime Achievement and Mentoring Award (page 12). Our current commitment is exemplified by the 6th Annual UCLA-Mellinkoff Gastroenterology and Hepatology Symposium (page 14), as well as the CURE Annual Research Meeting and Poster Session (page 16). You will also read about a team headed by Dr. Folasade May that won a prestigious award from the American College of Gastroenterology for its video promoting colorectal cancer screening (page 12).

After reading this issue of Beyond the Scope, we hope you will agree that great progress is being made in our laboratories, clinics and educational settings as we continue to strive to improve the lives of patients with IBD and other digestive disorders.
The sharp increase in the incidence of inflammatory bowel disease (IBD) – up as much as 20 percent over the last two decades – suggests that something more than genetics is involved, and that environmental factors must be playing a pivotal role in IBD pathogenesis. Both ulcerative colitis and Crohn’s disease are multifactorial, involving a combination of genetic factors, changes in immune cells, and alterations in the composition of bacteria in the gut. The environmental contributors to IBD have been studied far less extensively than the genetic and mechanistic pathways, but they are no less important to the effort to combat these diseases.

IBD emerged in Western countries through the middle of the 20th century, and only recently began to be seen at significant levels in developing nations such as China and India, suggesting that industrialization and the Westernization of lifestyle might be playing a role. Based on this hypothesis, urbanization, changes in diet, antibiotics, hygiene status, microbial exposures and pollution have all been implicated as potential environmental risk factors for IBD. Some of these associations are now supported by data. Several studies have shown positive associations between antibiotic use early in life and a greater risk for IBD among Western populations. Epidemiologic studies have consistently shown that IBD is more common in urban centers. The effect of urban environments on disease risk is particularly apparent in countries that have experienced industrialization and Westernization over the past few decades. And finally, evidence indicates that the composition of the intestinal microbiota can influence susceptibility to IBD. Dietary changes cause alterations in the microbiota, which, in turn, can lead to an aberrant intestinal immune response and eventually IBD. A pediatric study by Amre et al. reported an inverse association between intake of fruits and vegetables and Crohn’s disease risk.

Given the significant increase in IBD incidence over a short period of time, it’s clear that a combination of environmental factors is driving the change. Importantly, the molecular and cellular mechanisms affected by something as dynamic as our environment have to themselves be dynamic and susceptible to environmental influences. This points to a key role for the microbiome and the epigenome.

The articles that follow in this issue of Beyond the Scope focus on the work of our division faculty in elucidating how the environment affects the incidence and development of IBD through changes in the gut bacteria (microbiome), as well as through changes in microRNAs, long non-coding RNAs, DNA methylation and chromatin modifications (epigenome). We also look at the important and underappreciated connection between IBD and the brain (neurome).

Learning about environmental factors and how they affect the microbiome, epigenome and neurome is contributing to a better understanding of the pathogenesis of IBD. But more than that, the promise of this research is that unlike some of the other contributors to IBD, these factors can be targeted therapeutically, leading to new and better treatments for this growing population of patients.
The substantial increase in inflammatory bowel disease (IBD) incidence over the last decade suggests that environmental factors might play a major role in IBD pathogenesis. “Genetic alterations can’t explain the sharp rise in the number of cases we are seeing,” notes Dimitrios Iliopoulos, PhD, MBA, associate professor of medicine in the Vatche and Tamar Manoukian Division of Digestive Diseases and director of the division’s Center for Systems Biomedicine. Dr. Iliopoulos notes that only about 5 percent of IBD patients harbor genetic mutations, and the majority of the IBD single-nucleotide polymorphisms identified by large genome-wide association studies are located in regulatory areas. This points to the involvement of epigenetic alterations in triggering the disease – and the potential for epigenetic drugs to bring therapeutic benefits to IBD patients.

Epigenetic alterations – environmentally induced changes in the expression and function of genes without any modification in the DNA sequence – are known to play an important role in cancer, Dr. Iliopoulos says. Based on the findings from epigenomic research, several drugs targeting epigenetic pathways have been approved and are being used to treat cancer patients. But the epigenome hasn’t been studied extensively in IBD. “We don’t know yet how important it is, or whether new or existing epigenetic drugs might prove to be beneficial for IBD patients,” Dr. Iliopoulos says. Led by Dr. Iliopoulos as well as Drs. Charalabos “Harry” Pothoulakis and David Padua, UCLA has emerged as a national leader in investigating the role of the epigenome in IBD pathogenesis.

There are three subgroups of epigenetic alterations: non-coding RNAs (microRNAs and long non-coding RNAs), which are RNA molecules that are not translated into proteins, but act and function as RNAs; DNA methylation, in which gene expression is suppressed as a result of methyl groups being added to the DNA molecule –
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typically in the promoter, or regulatory, area of the genes; and changes at the chromatin level as a result of alterations in the tails of histones — which, together with DNA, are packed into the structures called nucleosomes that make up human chromosomes. Dr. Iliopoulos’ group is focusing on the role of DNA methylation and histone modifications in IBD pathogenesis, with an eye toward potential therapeutic targets.

Evidence from other labs as well as from Dr. Iliopoulos and his team suggests a link between DNA methylation and the development of IBD. Recent epigenetic profiling studies of colonic tissues in IBD patients have identified DNA methylation signatures for both ulcerative colitis and Crohn’s disease patients. Dr. Iliopoulos and his colleagues have identified an interplay between various epigenetic mechanisms and IBD pathogenesis. Specifically, in a paper published in the journal *Gastroenterology*, they showed that in pediatric patients with ulcerative colitis, microRNA-124 is epigenetically silenced through DNA methylation, resulting in activation of the IL6/STAT3 inflammatory pathway.

On the other hand, few molecular studies have examined the role of histone modifications in the development of IBD, Dr. Iliopoulos notes, although there are hints that they may be important to the process. A recent study of IBD-associated fibrosis found that chromatin modifications are linked with transcriptional activation of type 1 collagen gene expression, suggesting that epigenetic changes are involved in intestinal fibrogenesis. Other studies have reported that genes in the histone deacetylase (HDAC) are altered in IBD patients.

Two factors are responsible for the small number of studies related to histone regulation of IBD pathobiology, Dr. Iliopoulos explains. First, the methodology to purify chromatin from IBD colonic biopsies and, more generally, human tissues has yet to be optimized. More importantly, there are hundreds of combinations of histone modifications, making it difficult to find the right ones to study and determine their significance to the development of a human disease.

Dr. Iliopoulos believes the field of artificial intelligence can be used to overcome that obstacle. “A machine learning algorithm is needed to identify patterns in histone modifications and then group these patterns into specific histone states,” he explains. The Human Epigenome Consortium recently evaluated the human epigenomes of III individuals, and through a machine learning process organized all of the epigenetic alterations into 15 histone states. Based on this algorithm, Dr. Iliopoulos’ group has identified the histone state related to IBD pathogenesis and found novel epigenetic factors that are related IBD pathogenesis, and thus could potentially be targeted therapeutically. The findings were presented at the Digestive Disease Week 2017 meeting in Chicago by Dr. Marina Koutsioumpa, a postdoctoral fellow in Dr. Iliopoulos’ laboratory.

Multiple drugs are on the market and in clinical trials targeting epigenetic factors, Dr. Iliopoulos notes. These include DNA methyltransferase (DNMT) inhibitors such as azacitidine (Vidaza) and decitabine (Dacogen) that have been approved by the U.S. Food and Drug Administration (FDA) and are currently used in cancer patients; HDAC inhibitors such as vorinostat (Zolinza) and romidepsin (Istodax) that were more recently FDA-approved for the treatment of lymphomas; and histone methyltransferase inhibitors targeting EZH2 and G9a chromatin factors, which are in clinical development. “All of these drugs have the potential to be evaluated to see if they could have therapeutic value for IBD patients,” Dr. Iliopoulos says.

He points out that a major problem with these epigenetic therapies is the potential toxicity resulting from the fact that they target important genes that are also in healthy cells. “It is important to start developing more targeted epigenetic therapeutics that could affect specific epigenetic and immune-related factors and evaluate their efficacy in IBD animal models before we could move into the clinical testing,” Dr. Iliopoulos says. “But the bottom line is that we now have evidence that there are epigenetic changes in IBD patients, and based on these findings we have shown in animal models that epigenetic drugs have the ability to suppress inflammation and the development of IBD. This raises the possibility of a whole new area of potential therapies for IBD patients in the near future.”
One of the fastest-growing areas of biomedical science is the field of epigenetics – alterations in gene expression that do not involve changes in the DNA. These environmentally induced modifications are of particular interest to investigators looking to find effective new strategies for treating inflammatory bowel disease (IBD). In the laboratory of Charalabos “Harry” Pothoulakis, MD, the Eli and Edythe Broad Chair in Medicine and director of basic research for the UCLA Center for Inflammatory Bowel Diseases in the Vatche and Tamar Manoukian Division of Digestive Diseases, one of the major areas of focus is on a key player in the epigenetic response, microRNAs – small RNA molecules capable of regulating the function of multiple genes. Dr. Pothoulakis and his colleagues are international leaders in describing the role of microRNAs in IBD, and have developed strategies that show promise in being transferred to the clinic.

At the UCLA Center for Inflammatory Bowel Diseases, researchers focus on multiple aspects of IBD pathophysiology, diagnosis and therapy. This includes the role of neuropeptides and hormones in the mediation of inflammation and post-inflammation healing in IBD and the role of fat in the obese state in IBD pathogenesis – given that neuropeptides and hormones regulate appetite and metabolism, and their interactions with fat tissue represent important components of the inflammatory response in IBD.

The laboratory of Dr. Pothoulakis is also a world leader in studying the importance of microRNA-related changes in the IBD intestine and the importance of neuropeptides to this process, working closely with researchers in the UCLA Center for Systems Biomedicine, which is also part of the division.

“MicroRNAs are a very clever way for the host to inhibit the function of our genes,” Dr. Pothoulakis explains. He notes that scientists now understand the role of approximately 25,000 genes in the human body, and antagonists to these genes have been developed to inhibit their expression when they go awry. “We have only about 1,500 microRNAs to regulate these 25,000 genes,” Dr. Pothoulakis says. “So if we can use technologies that can inhibit certain microRNAs – or, when desirable, overexpress them, depending on the gene or genes they regulate – we are able to alter the inflammatory response.”

Nearly a decade ago, researchers found altered expression of microRNAs in tissues of patients with IBD. Dr. Pothoulakis was a pioneer in linking microRNA expression with neuropeptides and hormones known to be involved in the inflammatory response. His research group then led the way in showing the therapeutic potential – demonstrating that inhibiting or overexpressing these microRNAs can tamp down the
inflammatory response, as well as identifying the downstream targets of these activities.

More recently, Dr. Pothoulakis and colleagues have identified several microRNAs that are activated in the colonic mucosa of IBD patients in response to certain neuropeptides and hormones. They have made oligonucleotide-based, chemically-modified antagonists to these microRNAs and have shown in an IBD animal model that when introduced into the colon, blocking these microRNAs can inhibit the inflammatory response. They have also produced data supporting the efficacy of these antagonists in human biopsies – a critical step on the way to clinical trials with IBD patients.

Publishing in the journal Gut in 2015, Dr. Pothoulakis’ group demonstrated that the microRNA 133α is overexpressed in the colonic tissues of ulcerative colitis patients, and that it regulates the inflammatory signaling of neurotensin, a neuropeptide associated with colonic inflammation. This suggested that targeting the microRNA 133α could be an effective new strategy for a subset of IBD patients. Then in 2016, Dr. Pothoulakis and colleagues described in the Journal of Immunology a second important microRNA in IBD, microRNA-210, that plays a pro-inflammatory role in the development of colitis. The researchers found a network by which neurotensin regulates microRNA-210 as well as angiogenesis, an important aspect of the inflammatory response of IBD patients. This observation provided an additional therapeutic target.

Dr. Pothoulakis’ lab has also found that another neuropeptide, substance P, which mediates both pain and inflammation in humans, plays a critical role in the development of colitis. Reporting in Cellular and Molecular Gastroenterology and Hepatology in 2015, his group showed that when microRNA 221-5p is overexpressed by substance P, it targets the interleukin-6 receptor and, as a result, inhibits the inflammatory response. “All of these studies suggest that as we come up with specific microRNAs that are regulated differentially in IBD, we can either inhibit them if they promote colitis, as in the case of 133α and 210, or promote overexpression when they inhibit colitis, as in the case of 221-5p,” Dr. Pothoulakis explains.

“The advantage of our approach is that by giving an oligonucleotide-based antagonist intra-colonically (enema) to block or promote these microRNAs, we most likely can avoid the side effects associated with most of our current IBD therapies, which tend to be absorbed into the general circulation,” Dr. Pothoulakis adds. In addition, he notes, the strategy offers the potential for IBD clinicians to move toward precision medicine by looking at the biopsies of patients to see whether they have increased expression of these microRNAs, then using the antagonists only in the patients who have elevated levels — thus stratifying patients into groups where they are most likely to have a high rate of therapeutic response. “We are very encouraged by the response we are getting when we inhibit these microRNAs in IBD animal models and in human cells from the biopsies of patients,” Dr. Pothoulakis says. “This appears to be an approach with great potential for translation to the clinic.”
Physician-Scientist Receives Career Development Award to Explore Role of Non-Coding RNAs in IBD

As a physician-scientist who specializes in inflammatory bowel disease (IBD), David Padua, MD, PhD, has seen firsthand how the same drugs can affect IBD patients differently. “There are a lot of new IBD therapies in the pipeline, but the disease is extremely complex,” notes Dr. Padua, an assistant professor in the Vatche and Tamar Manoukian Division of Digestive Diseases. “We have to better understand the mechanisms that govern how this disease affects different patients in order to come up with more effective therapies and diagnostic tools.”

Dr. Padua is taking an approach that has not received a great deal of attention in IBD — studying the role of long non-coding RNAs (lncRNA) — RNA molecules with a length of 200 or more nucleotides that don’t encode proteins — in the inflammation process that characterizes the disease. “This is an area of biology that can help to give us a more complete picture of how IBD becomes a problem for these patients,” Dr. Padua explains. “By learning in the lab about the mechanisms of these non-coding RNAs, we’re laying a foundation that we hope will ultimately help to identify new drug targets for this disease process.”

IBD research has generally focused on RNAs transcribed as protein-coding genes, but the vast majority of DNA is transcribed as non-coding RNA, Dr. Padua notes. Cancer researchers have studied non-coding RNA for a number of years. “We can take many of the lessons that have been learned from cancer biology and apply them to IBD,” Dr. Padua says. For example, he explains, cancer researchers have reported on partner genes that certain
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non-coding RNAs function with, and these binding proteins and other downstream targets can be applied in IBD research.

More directly, Dr. Padua and colleagues can see how genes they are interested in have been studied in the context of cancer. As an example, Dr. Padua is interested in the role of the IncRNA gene CDKn2B antisense 1 in IBD. Given the gene’s impact on cell proliferation, researchers have learned about partner genes that bind with CDKn2B antisense 1 in colon cancer, and how these genes enable the cells to grow more efficiently with this non-coding RNA. “Now, when we look at it in the context of IBD, we have some guidelines,” Dr. Padua says. “We know that this gene has interacted with this other gene in another context, and we can see if that’s the case in IBD. Otherwise, we would be flying blind with a lot of these non-coding RNAs, because there isn’t that much known about a lot of them.”

The promise of Dr. Padua’s research was recently recognized by the Crohn’s & Colitis Foundation, which gave him a career development award to study non-coding RNAs in IBD. The grant provides three years of support and is designed to jump-start the career of talented young scientists. “I’m very grateful to the Crohn’s & Colitis Foundation for providing this level of support,” Dr. Padua says. “It’s exciting to have this recognition from the community that this is important work to move forward.”

The grant is funding Dr. Padua’s study of the gene interferon gamma antisense 1 (IFNGas1). Dr. Padua’s previous research had shown that this non-coding RNA can regulate the expression of interferon gamma, an important inflammatory cytokine. He and his colleagues are now looking more closely into that process as well as seeking to identify other mechanisms it can affect that influence IBD, and whether it offers a potential target for new drug development.

Dr. Padua takes a multi-system approach to studying IBD. He has in vitro studies within colon cells, and uses high-throughput technologies to learn more about the cell-signaling mechanisms that regulate IBD. His group is also looking at mouse models of the IBD process in an effort to understand these mechanisms in a more complex organism. Finally, Dr. Padua is applying the findings to his patients in order to develop more personalized medicine approaches to understanding how these non-coding RNAs can affect the disease. This includes taking tissue samples from patients who are having different responses to a therapy in order to home in on the factors that might be responsible for the difference.

“One of the most exciting things about being at UCLA is that we have this ability to go from the broad, patient population level all the way down to cell-based assays, and in between,” Dr. Padua says. “One of the most exciting things about being at UCLA is that we have this ability to go from the broad, patient population level all the way down to cell-based assays, and in between,” Dr. Padua says. “We have weekly meetings where all of us who are studying IBD get together to discuss our research, give each other ideas and share resources.”

Until recently, technical hurdles prevented RNA-based treatments from advancing to clinical trials, but that has changed in the last several years, and more than 100 clinical trials with RNA-based drugs have been launched. “There is now a big push by the pharmaceutical industry to develop these therapies for a host of different diseases,” Dr. Padua says. “My vision is that we will be able to identify key factors for inflammatory bowel disease and use them as drug targets in the near future.”
Inflammatory bowel disease (IBD) has long puzzled scientists and clinicians because of the lack of an obvious cause for the chronic inflammation. Research has focused on what differentiates the immune profiles of IBD patients from those without the disease, and more recently has broadened to include not only immune cells, but also epithelial cells that line the intestine as well as the network of other cell types that regulate the epithelial and immune cells. The recent explosion in research on the microbiome — the trillions of bacteria and other organisms that live within us — has drawn considerable attention to the role of gut bacteria in triggering the inflammatory process.

Jonathan P. Jacobs, MD, PhD, assistant professor in the Vatche and Tamar Division of Digestive Diseases, studies the impact of the intestinal microbiome on IBD. Dr. Jacobs notes that a fast-growing body of evidence is contributing to a better understanding of the role of gut bacteria in IBD pathophysiology. The evidence comes from both clinical and animal studies. “IBD patients have a distinct composition of their microbiome, and there is evidence that factors that change the microbiome can influence risk and severity of IBD. For instance, some people with IBD get better with antibiotics, there are some associations between diet and IBD incidence, and early-life antibiotics may affect IBD risk,” Dr. Jacobs explains. In addition, he notes, of the more than 200 genes that have been found to be associated with IBD, many affect how immune cells respond to gut bacteria, suggesting an important role for these bacteria in the development of the disease.

Animal studies have provided further evidence. IBD doesn’t develop in mouse models of the disease in the absence of bacteria, and the severity of IBD varies depending upon which bacteria are introduced into the mice, Dr. Jacobs notes. Studies have also shown that altering certain genes in mice changes their bacteria, and that the resulting bacterial change can increase susceptibility to IBD – a susceptibility that can be transferred to other mice through the bacteria. “It’s now believed that some gut bacteria can instigate disease in genetically vulnerable people, which creates new opportunities for therapies that might dampen inflammation by changing the bacteria or the bacterial signals,” Dr. Jacobs says.

In his lab, Dr. Jacobs and his colleagues are studying the role of the microbiome in the initial development of IBD. “Our hypothesis is that before IBD develops, there are changes in the microbiome that
create a vulnerable environment,” Dr. Jacobs explains. “The healthy gut ecosystem may go through various stages of abnormality, or dysbiosis, which could then make people vulnerable to developing diseases such as IBD.”

In a study recently published in the journal *Cellular and Molecular Gastroenterology and Hepatology* (CMGH), Dr. Jacobs provided the first evidence that siblings and parents of IBD patients can have a microbial profile that resembles that of IBD patients in remission — which Dr. Jacobs postulates is a pre-disease risk state. “The idea is that microbial changes associated with IBD can actually occur in the absence of disease, which we believe represents an intermediate stage in disease pathogenesis,” Dr. Jacobs says. “This is associated with increased susceptibility but without the full set of conditions for IBD to develop.”

In support of that conclusion, Dr. Jacobs also found that family members of IBD patients with the suspected pre-disease microbial state were more likely to have increased levels of a marker of intestinal inflammation. His group is following up on that research by trying to move from association studies in humans to mechanistic studies in animal models to establish causation. “We want to see whether these changes that occur in the absence of disease increase vulnerability to mouse models of IBD triggered by genetic factors,” Dr. Jacobs explains. The ongoing study is funded by the Crohn’s & Colitis Foundation.

“Ultimately, we might be able to prevent IBD from developing in those at risk using approaches such as dietary modifications or selective antimicrobials that push their microbiome to a more healthy state,” Dr. Jacobs says. “We could also apply the same principles to develop treatment strategies that modify the microbiome of IBD patients in clinical remission to reduce the risk of flare-ups of the disease.”

The potential for changes in the intestinal microbiota to have a therapeutic effect on IBD patients is exciting because it wouldn’t require changing the immune system. “Existing treatments have targeted specific immune cells or the molecules they make so that they are less able to perpetuate inflammation, but there is always some risk that comes with suppressing the immune system,” Dr. Jacobs says. “Also, many IBD patients do not respond to the current treatment options. Once we fully understand these microbial pathways in IBD, new drugs could be developed that improve treatment success and reduce side effects by targeting bacteria rather than our own cells.”
Growing Attention Paid to Links Between IBD and the Nervous System

What role do brain alterations play in inflammatory bowel disease (IBD)? Interactions between IBD and the nervous system – the so-called IBD neurome – are drawing a growing amount of attention from IBD researchers and funding agencies, and gaining a better understanding of these relationships has major therapeutic implications, according to Emeran A. Mayer, MD, PhD, professor in the Vatche and Tamar Division of Digestive Diseases and director of the division’s G. Oppenheimer Center for Neurobiology of Stress and Resilience.

That chronic inflammation in the body affects the brain has been shown, for example, from studies of patients with rheumatoid arthritis, as well as from studies involving animal models of colitis and patients with IBD, Dr. Mayer notes. He points out that approximately half of the brain cells are glial, immune-like cells that can be activated in the body by various mechanisms – including activated immune cells passing through the blood-brain barrier (so called “rolling”), cytokines and other pro-inflammatory molecules. “A host of mechanisms have been described by which the brain can receive signals from gut inflammation, engaging the glial cells within the brain, which in turn produce cytokines that affect the actual nerve cells within the brain,” Dr. Mayer says.

Fatigue and a general lack of well-being are common symptoms of IBD patients that can be linked to this neuro-inflammation in the brain, Dr. Mayer explains. He notes that when patients are treated with biologics such as tumor necrosis factor (TNF) alpha antibodies, some of their symptoms like brain fog or fatigue often disappear within 24 hours, long before there is any change in the gut inflammation. This is thought to be because blocking TNF-alpha receptors in blood vessels within the brain reduces neuro-inflammation, Dr. Mayer says.

Gut microbes, which are known to be altered within IBD, are also clearly sending signals to the brain, Dr. Mayer continues. “For a subset of Crohn’s disease patients – about 30-40 percent – when they go into clinical remission on traditional therapy, they still experience symptoms such as pain and altered bowel habits, even when an endoscopy shows no inflammation,” Dr. Mayer says. “While the mechanisms underlying these persistent symptoms are currently unknown, altered gut microbial signaling to the brain is a plausible hypothesis.”

The gut-brain influence goes the other way as well, Dr. Mayer adds. “We have always known that stress plays an important role in triggering symptom flares in a significant proportion of IBD patients, and that during stress the brain can change various gut functions by modulating target cells in the gut, including the microbes,” he says.

The role of the brain in IBD has not been significantly studied, Dr. Mayer notes, but that has begun to change. The Crohn’s and Colitis Foundation has made research into how stress and diet contribute to IBD a major funding priority. “We are seeing a paradigm shift in IBD research,” Dr. Mayer says. “While researchers have not traditionally thought about...
the role of the nervous system, such a mechanism is now being recognized as an important factor in IBD pathophysiology."

Dr. Mayer, along with Dr. Jonathan P. Jacobs, assistant professor in the division, have recently submitted several grant applications to further investigate how factors in the gut – including inflammation and the metabolites from microbes – affect brain function and structure. Dr. Mayer has received funding from the National Institutes of Health (NIH) to use magnetic resonance imaging to provide an in-depth characterization of these factors in ulcerative colitis patients.

Drs. Mayer and Jacobs also recently submitted a grant to the NIH to study their hypothesis that the reason a subset of Crohn’s disease patients in mucosal remission continue to experience symptoms may be caused by similar brain gut mechanisms implicated in the pathophysiology of irritable bowel syndrome (IBS), in which gut microbes and their metabolites are acting on the brain. “There is an ongoing debate about why these 30-40 percent of IBD patients are resistant to the classic therapy,” Dr. Mayer says. “If we confirm our hypothesis that such persistent symptoms are not related to gut inflammation but to the nervous system, the therapeutic implications are clear – that there has to be more of a brain-directed component to the overall treatment.” Potentially, Dr. Mayer explains, some of the same therapeutic approaches that have been shown to be successful with IBS patients, including mindfulness meditation, cognitive behavioral therapy, and centrally acting medications, could provide relief to Crohn’s disease patients for whom current treatment has been unsatisfactory in the form of adjuvant therapies.

“When you talk to IBD patients, many will all confirm that the brain and emotional factors play a big role in their symptoms,” Dr. Mayer says. “It could be that this is multifactorial – that the inflammation itself changes brain function and contributes to the symptom burden, or that the suffering from this disease makes people anxious and depressed. But nearly every patient I have talked to would confirm this important link between the brain and IBD, and they’re thankful that this is finally coming into focus with regard to conventional treatment.”
**Dr. Vay Liang W. “Bill” Go Receives Lifetime Achievement and Mentoring Award**

Vay Liang W. “Bill” Go, MD, distinguished professor in the Vatche and Tamar Division of Digestive Diseases and co-director of the UCLA Aghi Hirshberg Center for Pancreatic Diseases, received the 2017 Lifetime Achievement and Mentoring Award from the Collaborative Alliance for Pancreatic Education and Research (CAPER) at the annual meeting of PancreasFest in Pittsburgh last July.

Dr. Go, who serves as editor-in-chief of the journal *Pancreas* and co-founded the American Pancreatic Association, served as executive chairman of the UCLA Department of Medicine from 1988 to 1992 and went on to co-found the UCLA Center for Human Nutrition in 1994. He has co-authored more than 400 peer-reviewed manuscripts and mentored and trained more than 70 fellows in gastroenterology, nutrition, endocrinology and pancreatology over the course of his career, many of whom have attained leadership roles in their respective fields. He has also received numerous national and international awards. Prior to coming to UCLA in 1988, Dr. Go served as a professor of medicine at the Mayo Clinic and was director of the Division of Digestive Diseases and Nutrition for the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health.

At the award ceremony, Dr. Go presented on his five-decade journey as a mentee, mentor and reverse mentor in academic medicine. “I am honored to receive an award that highlights the importance of mentorship,” Dr. Go says. “As scientists we are all deeply indebted to the people who trained and mentored us, and I am pleased to know that so many of my trainees have gone on to successful careers and become mentors themselves. Reverse mentorship provided by my trainees is one of the most rewarding part of my career.”

**Division-Led Team Honored for Video on Colorectal Cancer Screening**

Folasade P. May, MD, PhD, MPhil, physician and health services researcher and her team in the UCLA Vatche and Tamar Manoukian Division of Digestive Diseases, was honored in October at the annual meeting of the American College of Gastroenterology (ACG) for its video designed to promote colorectal cancer screening.

The UCLA group won first place in the Best Video by an Academic Center category at ACG’s third annual SCOPY Awards (Service Award for Colorectal Cancer Outreach, Prevention & Year-Round Excellence), which recognizes the achievements of ACG members in their community engagement, education and awareness efforts for colorectal cancer prevention. ACG members are invited to submit examples of projects and programs that demonstrate outstanding creativity and commitment to spreading the potentially lifesaving message of the importance of colorectal cancer screening and prevention.

The winning video by Dr. May’s team features a conversation between a provider and a patient that dispels myths about colorectal cancer and encourages patients to get screened. The video will be further developed toward the ultimate goal of showing it to UCLA patients as part of the UCLA Colon Health Program’s initiative to bring screening rates up to 80 percent, in conjunction with the national goal of 80 percent by 2018 for colorectal cancer screening.

“It’s a great honor to be recognized by the American College of Gastroenterology for our team’s effort to increase awareness about colorectal cancer, and to emphasize that screening is an easy way to save lives,” Dr. May says.

In addition to Dr. May, the team that created the video includes Drs. Dean Ehrlich, Shelley Schwartz, and Nasim Assar and Anna Dermenchyan, RN, all from the UCLA Department of Medicine.
A National Institutes of Health (NIH)-funded consortium headed by Yvette Taché, PhD, distinguished professor of medicine in the Vatche and Tamar Manoukian Division of Digestive Diseases, will take advantage of new technologies to provide the first comprehensive and detailed structural and functional mapping of the nervous system as it relates to colonic function in humans and the pig, a large animal model with structural and physiological similarities to humans. The three-year, $7.5 million grant is expected to lay the groundwork for the development of a new class of treatments — electroceutical interventions — for colonic disorders.

The consortium grant is part of the NIH’s Stimulating Peripheral Activity to Relieve Conditions (SPARC) program, which is expected to provide approximately $238 million in funding over a five-year period in an effort to map the body’s electrical wiring and develop devices that will allow for the therapeutic stimulation of those nerves. More than two-dozen multidisciplinary teams are being funded through SPARC, including groups studying other organs such as the heart, lung and spleen, to gain new insights into how peripheral nerves control internal organ function, and how modulation of these signals can treat common conditions and diseases.

Dr. Taché notes that the colon is the site of multiple disorders — including chronic constipation, diarrhea, diverticulitis, irritable bowel syndrome (IBS), inflammatory bowel diseases (IBD), Clostridium difficile colitis, cancer, Parkinson's associated dysmotility, and age-related pelvic dysfunction — that are leading causes of morbidity and mortality, at a high financial cost. Given the important role of the nervous system in regulating colonic function, there has long been an interest in understanding the neurochemical and electrophysiological properties, cell physiology, and functional roles of colonic enteric neurons and cellular interaction with the parasympathetic, sympathetic and sensory systems. Until recently, though, these data could be obtained only from small animal studies, which has hampered the development of effective therapies. That has changed with advances in tools that include tissue clearing (CLARITY), high-resolution confocal microscopy, light sheet microscopy, 3D imaging, molecular phenotyping using laser capture microdissection (LCM), RNA-sequencing and viral tracing methodologies.

The UCLA-led SPARC team will use these sophisticated technological and imaging approaches to map the nerves and functional circuitries, setting the foundation for the project’s second phase, in which researchers will run therapeutic assays under pathophysiological conditions in an effort to develop electroceutical interventions to treat colonic disorders. Dr. Taché leads a multidisciplinary team of top investigators using state-of-the-art methodologies both from UCLA — where researchers from five departments are represented — and from five outside universities. In addition to the collaborations within the consortium, Dr. Taché’s group will meet regularly with other SPARC consortiums to exchange ideas and share data.

The ambitious study represents a culmination of work Dr. Taché has engaged in since 1980, when she began pioneering research in the field of brain-gut interactions. "I became very interested early on in autonomic nerve activity, which connects the brain, spinal cord and visceral organs related to the GI tract," she says. "So the opportunity to gather a group of investigators with world-class expertise to tackle nerve mapping so that we can move to the pathophysiology is very exciting to me."
The 6th Annual UCLA-Mellinkoff Gastroenterology and Hepatology Symposium has been designed as an interactive, case-based learning activity to educate healthcare professionals on the evaluation and management of patients with gastrointestinal disorders. Audience participation is encouraged through panel discussions and audience response system. The hands-on session provides a valuable learning opportunity, though no CME credit will be issued for participation in this session.

Registration and Course Information

CME – go to www.cme.ucla.edu/courses, click on 6th Annual UCLA-Mellinkoff Gastroenterology and Hepatology Symposium.

Contact Hours – go to www.regonline.com/ UCLA-Mellinkoff-GIHepatology2018

Overnight Accommodations

A limited block of rooms, at a special rate of $285 + tax (deluxe) and $325 + tax (studio suite), has been reserved at The Beverly Hilton. To receive the special rate, you must make your reservation before the room block is filled and by the expiration date of February 12, 2018. To reserve a room, call 1-800-HILTONS and ask for the “UCLA Digestive Diseases” block. Or make a reservation online at https://aws.passkey.com/e/49288619

For more information about the hotel, visit www.beverlyhilton.com
**Friday, March 9**

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

**Functional Bowel Disease**  
Moderator: Lynn Shapiro Connolly, MD, MSCR, UCLA

8:00 am  An Interactive Case-based Discussion  
- Irritable Bowel Syndrome (IBS-C and IBS-D)  
- Functional Dyspssia  
- Gas, Bloating and Cramping  
- Functional Diarrhea and Constipation  
- Role of Diet in These Symptoms and Syndromes  
Panel: Lin Chang, MD, UCLA, Nancee Jaffe, MS, RDN, UCLA, Emeran A. Mayer, MD, PhD, UCLA and Kirsten Tillisch, MD, UCLA

10:00 am  Break

**Liver Disorders**  
Moderator: Mohamed El Kabany, MD, UCLA

10:20 am  Hepatitis C: The Final Chapter  
Sammy Saab, MD, MPH, UCLA

10:40 am  Chronic Hepatitis B: A Search for a Cure  
Steven-Huy Han, MD, UCLA

11:00 am  Fat, Fat and More Fat: Updates  
Alireza Sedarat, MD, UCLA

11:20 am  Lunch

11:40 am  Autoimmune Liver Disease  
Gina Choi, MD, UCLA

12:10 pm  Autoimmune Liver Disease  
Panel including Francisco Durazo, MD, UCLA

**Pancreatobiliary Disease**  
Moderator: V. Raman Muthusamy, MD, UCLA

1:00 pm  Maximizing ERCP Cannulation Efficiency  
and Minimizing Trauma  
Michael L. Kochman, MD, University of Pennsylvania

1:20 pm  Autoimmune Cholangiopathy  
and Pancreatitis  
Alineza Sedarat, MD, UCLA

1:40 pm  Acute and Chronic Pancreatitis:  
When to Refer to Surgery  
Timothy R. Donahue, MD, UCLA

2:00 pm  The Evolving Role of EUS  
in Pancreatic Disease  
Stephen Kim, MD, UCLA

2:20 pm  Cases and Q & A  
Panel

2:40 pm  Break

**Women’s GI Issues**  
Moderator: Rimma Shaposhnikov, MD, UCLA

3:00 pm  The Use of Common GI Medications  
in Pregnancy  
Rimma Shaposhnikov, MD, UCLA

3:20 pm  Bowel Control and the Pelvis of Pregnancy:  
Function Disorders of the Ano-rectum  
in Women  
Christopher M. Tamey, MD, UCLA

3:40 pm  Hemorrhoids and Fissures: Diagnosis  
and Management of Complications  
Anne Y. Lin, MD, MSHS, UCLA

4:00 pm  Challenging Patient Cases and Q & A  
Panel

4:20 pm  Adjourn Didactic Session

4:30 pm  Hands-On Session – No CME Credit*

5:30 pm  Adjourn Hands-On Session

**Saturday, March 10**

7:00 am  Registration and Breakfast

**7:55 am  Welcoming Remarks**  
Eric Eastrallan, MD, MPH, UCLA

8:00 am  Inflammatory Bowel Diseases  
Moderator: Jenny Sauk, MD, UCLA

8:30 am  An Interactive Case-based Discussion  
Crohn’s Disease  
- The Refractory Crohn’s Disease  
- Patient Failing Anti-TNF Therapy  
- Therapeutic Drug Monitoring  
- Management of Perianal Crohn’s Disease  
- Ulcerative Colitis  
- Counseling Patient on Risks/Benefits of Biologic Therapy  
- Recurrent C. difficile in Ulcerative Colitis  
- Steroid-Dependent Ulcerative Colitis  
- Refractory to Biologic Therapy  
Panel: Maria T. Abreu, MD, University of Miami, Daniel Honnes, MD, PhD, UCLA, David A. Schwartz, MD, Vanderbilt University

10:00 am  Break

**Improving Endoscopic Practice**  
Moderator: Stephen Kim, MD, UCLA

10:20 am  Transitioning to an All Anesthesia  
Endoscopic Unit: Lessons Learned  
Kia Kianusch, MD, UCLA

10:40 am  Protecting the Endoscopist: Ergonomics  
in the Endoscopy Unit  
Amandeep Shergill, MD, MS, UC San Francisco

11:00 am  Q & A

**Endoscopy Video Forum**  
Moderator: Bennett E. Roth, MD, UCLA

11:20 am  Primer on Common Techniques  
Panel: Stephen Kim, MD, UCLA, Michael L. Kochman, MD, U Penn, Amandeep Shergill, MD, MS, UCSF, V. Raman Muthusamy, MD, UCLA, Alineza Sedarat, MD, UCLA

**12:20 pm  Lunch**

**Esophageal Disorders**  
Moderator: Kevin Ghassemi, MD, UCLA

1:20 pm  Barrett’s Esophagus: An Update on Recently  
Developed Quality Metrics  
V. Raman Muthusamy, MD, UCLA

1:40 pm  Managing Esosinophilic Esophagitis: The  
Role of Diet, Medications and Endoscopy  
Kevin Ghassemi, MD, UCLA

2:00 pm  Esophageal Physiology Testing:  
Which Test to Use and When  
Jeffrey L. Conklin MD, UCLA

2:20 pm  Endoscopic Management of Upper GI Bleeding  
Dennis Jensen, MD, UCLA

2:40 pm  Cases and Q & A  
Panel

**3:00 pm  Break**

**Colorectal Cancer Screening: Improving Access and Quality**  
Moderator: Rajinder Kaushal, MD, UCLA

3:20 pm  Colorectal Cancer Screening: Achieving  
80% by ‘18 - How Close Are We?  
Folasade P. May, MD, PhD, MPH, UCLA

3:40 pm  A Primer on Colonoscopy Preparations  
and Diet  
Jason B. Samarasena, MD, UC Irvine

4:00 pm  Tips to Improve Your Ability to Detect,  
Inspect and Characterize Colon Polyps  
Stephen Kim, MD, UCLA

4:20 pm  Alternatives to Optical Colonoscopy for  
Screening: Virtual and Capsule Colonoscopy  
Amandeep Shergill, MD, MS, UC San Francisco

4:40 pm  Challenging Patient Cases and Q & A  
Panel

5:00 pm  Course Summary and Final Announcements  
V. Raman Muthusamy, MD, UCLA

5:05 pm  Adjourn

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*Friday, March 9, 4:30 – 5:30 pm  Complimentary Hands-on Session — All Attendees*

The hands-on session will provide a valuable learning opportunity, though no CME credit will be issued for this portion of the program. The hands-on session is complimentary. Please indicate on your registration form if you will be participating.

**Faculty Include:**  
Kevin Ghassemi, MD, UCLA, Stephen Kim, MD, UCLA, Michael L. Kochman, MD, U Penn, V. Raman Muthusamy, MD, UCLA, Alireza Sedarat, MD, UCLA, Amandeep Shergill, MD, MS, UC San Francisco
CURE Annual Research Meeting and Poster Session | March 23, 2018

UCLA Sunset Village on the Campus of UCLA, Covel Commons

Non-CME Program

Course Chair
Enrique Rozengurt, DVM, PhD, AGAF
Director, CURE: Digestive Diseases Research Center
Distinguished Professor, Vatche and Tamar Manoukian
Division of Digestive Diseases, Department of Medicine,
David Geffen School of Medicine at UCLA

Invited John H. Walsh Memorial Lecturer
Rodger A. Liddle, MD
Professor of Medicine
Duke University Medical Center

Meeting Information

Meeting Location
UCLA Sunset Village on the Campus of UCLA
Northwest Auditorium and the Carnesale Palisades Room
330 DeNeve Drive, Los Angeles, CA 90024

Conference Parking
Complimentary parking will be provided in Lot PSV. There will be an attendant at the gate to provide parking permits.

Registration Fee
$100 — Non-UCLA physicians
Complimentary — UCLA physicians, fellows and residents
Fee includes registration, breakfast, breaks and lunch. This is a non-CME program.

Refunds
Cancellations must be received in writing by Friday, March 9, 2018 and will be subject to $50 processing fee. No refunds will be granted after that date. If, for any reason, the course must be cancelled or rescheduled by CURE, a full refund will be provided.

Meeting Inquiries and Enrollment
Contact Jacqueline Ismen at jismen@mednet.ucla.edu or call (310) 312-9284 for more information or to receive an enrollment form.
### Agenda

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Speaker(s)</th>
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<tbody>
<tr>
<td>7:45 am</td>
<td>Registration and Breakfast</td>
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<tr>
<td>8:30 am</td>
<td>Welcoming Remarks</td>
<td>Joseph Pisegna, MD, UCLA</td>
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<td></td>
<td><strong>Session I: Clinical/Translational Session</strong></td>
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<tr>
<td>8:35 am</td>
<td>Clinical Implications of Brain-Gut Microbiome Interactions</td>
<td>Emeran A. Mayer, MD, PhD, UCLA</td>
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<tr>
<td>9:05 am</td>
<td>Influenza Infection in the Lungs Affects Microbiota in the Gut Through Type I Interferon</td>
<td>Genhong Chen, PhD, UCLA</td>
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<tr>
<td>9:35 am</td>
<td>Break</td>
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<tr>
<td></td>
<td><strong>Session II: Translational/Basic Science Session</strong></td>
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<tr>
<td>9:50 am</td>
<td>Bile Acid Metabolism Pathways in Health and Disease</td>
<td>Thomas Vallim, MSci, PhD, UCLA</td>
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<tr>
<td>10:20 am</td>
<td>Building the Gut in a Dish: Prospects for Modeling and Identifying New Therapies of GI Disorders</td>
<td>Martín G. Martín, MD, MPP, UCLA</td>
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<tr>
<td>10:50 am</td>
<td>Break</td>
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<tr>
<td>11:05 am</td>
<td>Remarks and the John H. Walsh Memorial Lecture</td>
<td>Eric Esrailian, MD, MPH, UCLA</td>
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<td>11:10 am</td>
<td>State of CURE</td>
<td>Enrique Rozengurt, DVM, PhD, AGAF, UCLA</td>
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<tr>
<td>11:25 am</td>
<td><strong>John H. Walsh Memorial Lecture</strong></td>
<td>The Gut Connectome and Implications for Disease</td>
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<td>12:30 pm</td>
<td>Lunch</td>
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<td><strong>Session III: Looking to the Future</strong></td>
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<tr>
<td>1:30 pm</td>
<td>Helicobacter Pylori and Gastric Injury</td>
<td>Elizabeth Marcus, MD, UCLA</td>
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<td>1:50 pm</td>
<td>The Role of Long Non-coding RNAs in Inflammatory Bowel Disease</td>
<td>David Padua, MD, PhD, UCLA</td>
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<td>2:10 pm</td>
<td>Brain Signatures in Obesity</td>
<td>Arpana Gupta, PhD, UCLA</td>
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<td>2:30 pm</td>
<td>Break</td>
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<tr>
<td>2:45 pm</td>
<td>Poster Session – Even-numbered Posters</td>
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<td>3:45 pm</td>
<td>Poster Session – Odd-numbered Posters</td>
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<tr>
<td>4:45 pm</td>
<td>Adjourn</td>
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### UCLA Course Faculty

- **Genhong Cheng, PhD**  
  Professor, Department of Microbiology, Immunology and Molecular Genetics  
  David Geffen School of Medicine at UCLA

- **Eric Esrailian, MD, MPH**  
  Co-Chief, Vatche and Tamar Manoukian Division of Digestive Diseases  
  Director, Melvin and Bren Simon Digestive Diseases Center  
  Lincy Foundation Chair in Clinical Gastroenterology  
  Health Sciences Associate Clinical Professor of Medicine  
  David Geffen School of Medicine at UCLA

- **Arpana Gupta, PhD**  
  Co-Director, Bioinformatics and Neuroimaging Core, G. Oppenheimer Center for Neurobiology of Stress and Resilience  
  Adjunct Assistant Professor  
  Vatche and Tamar Manoukian Division of Digestive Diseases  
  David Geffen School of Medicine at UCLA

- **Elizabeth Marcus, MD**  
  Assistant Professor of Pediatrics, Department of Pediatrics  
  Division of Pediatric Gastroenterology, Hepatology, and Nutrition  
  David Geffen School of Medicine at UCLA

- **Martín G. Martín, MD, MPP**  
  Associate Vice-Chair for Translational Research  
  Professor of Pediatric Gastroenterology and Nutrition  
  Department of Pediatrics  
  David Geffen School of Medicine at UCLA

- **Emeran A. Mayer, MD, PhD**  
  Director, G. Oppenheimer Center for Neurobiology of Stress and Resilience  
  Co-Director, CURE: Digestive Diseases Research Center  
  Professor of Medicine, Physiology and Psychiatry  
  Vatche and Tamar Manoukian Division of Digestive Diseases, David Geffen School of Medicine at UCLA

- **David Padua, MD, PhD**  
  Associate Director, UCLA GI Fellowship Program  
  Assistant Professor-in-Residence  
  Vatche and Tamar Manoukian Division of Digestive Diseases  
  David Geffen School of Medicine at UCLA

- **Thomas Vallim, MSci, PhD**  
  Assistant Professor  
  Department of Biological Chemistry and the Department of Medicine  
  Division of Cardiology  
  David Geffen School of Medicine at UCLA
UCLA Gastroenterology and GI Surgery among the best in the nation by *U.S. News & World Report* in its 2017-2018 survey. UCLA Health hospitals in Westwood and Santa Monica ranked No. 7 in the nation.