Welcome Remarks, **Joseph Pisegna, MD** Chief, Division of Gastroenterology and Hepatology VA and Professor of Medicine and Human Genetics Co-Chair and Member of the Organizing Committee.

**SESSION I: Clinical/Translational Session** (Moderators: **Lin Chang, MD** Vice-Chief, Professor of Medicine Vatche and Tamar Manoukian Division of Digestive Diseases David Geffen School of Medicine and **Dennis Jensen, MD** Professor of Medicine Vatche and Tamar Manoukian Division of Digestive Diseases David Geffen School of Medicine at UCLA)

**8:35 am - 9:35 am**

**Timothy Donahue, MD** Professor of Surgery and Molecular & Medical Pharmacology, Chief, Division of Surgical Oncology, Vice Chair, Surgical Cancer Care, David Geffen School of Medicine at UCLA

“Causes and consequences of interferon signaling in pancreatic cancer”

**Summary:** Pancreatic ductal adenocarcinomas (PDAC) are characterized by a high rate of KRAS mutation and an inflammatory microenvironment. The therapeutic vulnerabilities of PDAC linked to oncogenic KRAS signaling have been widely examined; however, the impact of inflammatory mediators on therapy response are less well defined. Interferons (IFN) are pleiotropic cytokines that regulate tumor cell expression of immune checkpoints and are linked to both chemotherapy and radiation resistance. Among TCGA solid tumor datasets, PDAC ranks highly in Type I IFN signaling with a range observed across tumors. We found that Type I IFNs in PDAC are produced by the tumor cells via the cytosolic DNA sensing cGAS/STING pathway. We further determined that type I IFNs increase the level of replication stress within tumor cells by increasing metabolic enzymes involved in nucleotide catabolism and deamination. This, in turn, creates a co-dependency on the replication stress response kinase Ataxia Telangiectasia and Rad3-related protein (ATR). Treatment of Type I IFN exposed PDAC cells with ATR inhibitors synergistically increased levels of DNA damage and sensitized cells to co-inhibition of PARP1. Collectively, our work begins to identify a “personalized” treatment approach for the substantial subgroup of PDAC patients with high intratumoral levels of Type I IFN signaling.

**9:05 am - 9:35 am**

**Peter Anton, MD,**
Professor of Medicine
Director: UCLA Center for HIV Prevention Research (CPR)
Director: CFAR Mucosal Immunology Core Laboratory (MICL)
Vatche & Tamar Manoukian Division of Digestive Diseases;
Department of Medicine
David Geffen School of Medicine at UCLA & UCLA AIDS Institute

“Recent advances in HIV transmission prevention and treatment”
Summary: Diseases and their target organs provide indices by which interventions can be measured as improvements back toward ‘normal’. Prevention efforts in healthy individuals are challenging in different ways: Efficacy trials are long; animal models frequently do not fully translate; characterizing ‘safety & ex vivo effects’ requires well-characterized ‘healthy’ indices given the absence of disease responses for comparison. As an example: HIV prevention in healthy individuals has focused on ensuring the delivery of presumed preventive levels of ART medications within the leading target cells (CD4 T lymphocytes) in the most vulnerable compartments (rectal>>vaginal) during vulnerable windows of exposure (coital-dependent/chronic). These efforts in pharmacokinetics (PK) and pharmacodynamics (PD) are often summarized as “getting the ‘right’ drug to the ‘right’ place at the ‘right’ time for the ‘right’ duration”; successful “targeting” only enhances this goal. These efforts have required characterization (durability, stability, reproducibility) of “normal ranges” of measured units in local tissues, cells and secreted fluids as well as new NIH/FDA-rectal mucosa toxicity grading tables for healthy adults. These validated “normal ranges” have provided meaningful context for exploratory/Phase 1 trials of safety and acceptability, especially when utilizing a FDA-approved agent using a new ‘route of drug administration’ and delivery vehicle formulation. These efforts provide normative ranges for comparison in pathogenesis studies of other diseases.

Break 9:35 am - 9:50 am
Break, Foyer, Northwest Auditorium

9:50 am - 10:50 am
SESSION II: Translational/Basic Science Session (Moderators: Joseph Pisegna, MD and Charalabos Pothoulakis, MD Professor of Medicine Vatche and Tamar Manoukian Division of Digestive Diseases, David Geffen School of Medicine at UCLA)

9:50 am - 10:20 am
Peter Tontonoz, MD, PhD
Professor, Department of Pathology and Laboratory Medicine, David Geffen School of Medicine at UCLA
“Cholesterol and phospholipid metabolism in intestinal homeostasis”

Summary: Phospholipids are important determinants of membrane biophysical properties, but the impact of membrane acyl chain composition on systemic metabolism is unknown. Here we demonstrate that the LXR-responsive phospholipid-remodeling enzyme Lpcat3 modulates hepatic lipoprotein production and intestinal fatty acid and cholesterol absorption and is required for survival on a high-fat diet. Lpcat3-dependent incorporation of polyunsaturated fatty acids into phospholipids is required for the triglyceride secretion from the liver and for efficient transport of dietary lipids into enterocytes. Furthermore, loss of Lpcat3 amplifies the production of gut hormones in response to high-fat feeding, contributing to the paradoxical cessation of food intake in the setting of starvation. We further reveal an unexpected link between membrane phospholipid remodeling and cholesterol biosynthesis, and we demonstrate that cholesterol itself acts as a mitogen for intestinal stem cell proliferation. Inhibition of Lpcat3 increases membrane saturation and stimulates PI3K/AKT activity and cholesterol biosynthesis, thereby driving intestinal stem cell proliferation. Pharmacologic inhibition of cholesterol synthesis normalizes crypt hyperproliferation in Lpcat3-deficient organoids and mice. Conversely, increasing cellular cholesterol content is sufficient to stimulate crypt organoid growth ex vivo, and providing excess exogenous cholesterol in the diet or driving endogenous cholesterol synthesis through SREBP-2 expression promotes intestinal stem cell proliferation in vivo. Finally, we show that disruption of Lpcat3-dependent
phospholipid and cholesterol homeostasis dramatically enhances tumor formation in ApcMin mice. These findings identify a dietary-responsive phospholipid-cholesterol axis as critical modulator of stem cell proliferation and tumorigenesis.

10:20 am - 10:50 am  
D. Leanne Jones, PhD  
Professor, Molecular, Cellular and Developmental Biology, UCLA  
“DNA methylation analysis reveals differences in aging between human small intestine and colon”

Summary: The epithelia of the intestine and colon turn over rapidly and are maintained by adult stem cells at the base of crypts. While the small intestine and colon have distinct, well-characterized physiological functions, it remains unclear if there are fundamental regional differences in stem cell behavior or region-dependent degenerative changes during aging. Mesenchyme-free organoids provide useful tools for investigating intestinal stem cell biology in vitro and have started to be utilized for investigating age-related changes in stem cell function. However, it is unknown whether organoids maintain hallmarks of age in the absence of an aging niche. Here we used the human 'epigenetic clock' as a biomarker of age to determine that stem cell derived organoids preserve DNA methylation-based aging profiles associated with the tissues and crypts from which they were derived. Unexpectedly, however, we find that the human small intestine exhibits striking epigenetic age reduction relative to colon, which occurs midlife, a difference preserved in cultured spheroids. Our data demonstrate significant regional differences in epigenetic aging in the human intestine that appear to be maintained in vitro.

Break 10:50 am - 11:05 am  
Break, Foyer, Northwest Auditorium

11:05 am - 12:30 pm  
Remarks and the John H. Walsh Memorial Lecturer

11:05 am - 11:10 am  
Eric Esrailian, MD, MPH, Chief, Vatche and Tamar Manoukian Division of Digestive Diseases, Associate Professor Department of Medicine David Geffen School of Medicine at UCLA

11:10 am - 11:25 am  
Enrique Rozengurt, DVM, PhD, AGAF Director, CURE: Digestive Diseases Research Center, Professor of Medicine, Vatche and Tamar Manoukian Division of Digestive Diseases, Department of Medicine David Geffen School of Medicine at UCLA

State of CURE

11:25 am - 12:25 pm  
John H. Walsh Memorial Lecture: Eugene Chang, MD, Eugene B. Chang, MD Martin Boyer Professor of Medicine, Director, Microbiome Medicine Program and IBD Translational Research Center. Knapp Center for Biomedical Discovery University of Chicago  
“Insights into Inflammatory Bowel Diseases through the lens of human and experimental models”

Summary: Inflammatory bowel diseases (IBD) are chronic, progressive diseases characterized by aberrant immune responses to environmental and gut microbial triggers in genetically susceptible hosts. Compelling clinical, genetic, and experimental data support the role of gut microbes in causing and sustaining these
diseases. In addition, our concepts of IBD have changed dramatically through advances in technologies and experimental and clinical model systems. Despite this, the study of microbes in human IBD remains descriptive and some of the most basic questions about the role of the gut microbiota in causing and perpetuating disease remain unanswered. The next phase of investigations of the gut microbiome in IBD should be guided by specific biological questions relevant to clinical observation and the natural history of the diseases. This approach will be essential for the eventual development of microbial, genetic, and biological metrics useful for individualized assessment of risk and improvement of clinical outcomes in IBD.

12:30 pm - 4:30 pm  
**Afternoon Session – Carnesale Commons Palisades Room**

12:30 pm - 1:30 pm  
**LUNCH – Carnesale Commons Palisades Room**

**SESSION III: Looking to the Future**  
(Moderator: Catia Sternini, MD, Professor of Medicine, Vatche and Tamar Manoukian Division of Digestive Diseases and Neurobiology, Co-Chair Organizing Committee) – **Palisades Room**

1:30 pm - 1:45 pm  
De-Chen Lin, PhD  
Assistant Professor, Division of Oncology, Department of Medicine, Cedars-Sinai Medical Center  
"Master transcription factors form inter-connected circuitry and dysregulate transcriptional network in esophageal cancer"

**Summary:** Malignant transformation is accompanied by locus-specific gains and losses in enhancer activity (especially super-enhancers) across the epigenome, profoundly rewiring the transcriptional network required for tumor development and progression. In this lecture, I will discuss how these transcriptional changes are orchestrated by master transcription factors in a cancer- and subtype-specific manner, as well as their impact on esophageal cancer biology.

1:45 pm - 2:00 pm  
Jill Hoffman, PhD  
Assistant Professor  
Vatche and Tamar Manoukian Division of Digestive Diseases  
David Geffen School of Medicine at UCLA  
"Corticotropin-releasing hormone mediated enteric glial cell function during colitis"

**Summary:** Inflammatory Bowel Disease (IBD) is a chronic relapsing inflammatory disorder of the gastrointestinal (GI) tract. The enteric nervous system (ENS) plays a critical role in orchestrating GI function during health and disease and enteric glial cells of the ENS are increasingly becoming recognized for their active roles during intestinal inflammation. The CRH family of neuropeptides and receptors is modulated in multiple cell types of the inflamed intestine, yet little is known regarding neuropeptide-mediated enteric glial cell function. Using a combination of *in vivo* and *in vitro* approaches, we are investigating CRHR2-mediated EGC responses during inflammation. Better understanding of the role of this receptor and overall enteric glial cell function during colitis could lead to targeted treatments to limit inflammation and promote remission during colitis.
Jennifer Fulcher, MD,
Assistant Professor in Residence,
Assistant Professor, Division of Infectious Diseases, Department of Medicine, David Geffen School of Medicine
“Behavioral influences on the rectal mucosal microenvironment: Implications for HIV”

Summary: Mucosal inflammation plays a pivotal role in HIV transmission as well as pathogenesis of chronic infection. Interactions between the intestinal microbiome and host mucosal immune system help regulate mucosal inflammatory states. HIV infection can alter the human intestinal microbiome; however, the extent to which behavioral factors drive these changes remains poorly defined. Our work has examined the effects of substance use and sex behavior on the microbiome during HIV infection, and we employed a high-dimensional covariate adjustment method to more specifically assess the effects of HIV on the microbiome. In addition, we have also examined the direct effects of substance use on mucosal inflammation. Collectively we show that drug use and sex behavior are important factors associated with intestinal dysbiosis and mucosal inflammation in at-risk and HIV-infected individuals, providing a biological basis for the associations between these risk behaviors and HIV.