

# KEYSTONE SYMPOSIA

on Molecular and Cellular Biology

## Fatty Liver Disease and Multi-System Complications (EK28)

Scientific Organizers: Jay D. Horton, Morris J. Birnbaum and Hannele Yki-Järvinen

Sponsored by Merck & Co., Inc. and Novo Nordisk A/S

## Hepatobiliary Cancers: Pathobiology and Translational Advances (EK29)

Scientific Organizers: Alphonse E. Sirica, Gregory J. Gores and Lopa Mishra

March 22-24, 2021 • Virtual at your computer

Supported by the Directors' Fund

### MONDAY, MARCH 22

#### Welcoming Remarks and Keynote Session (Joint) (8am Denver/Mountain Time Start)

\***Jay D. Horton**, University of Texas Southwestern Medical Center, USA

Session Chair

\***Alphonse E. Sirica**, Virginia Commonwealth University, USA

Session Chair

**Helen H. Hobbs**, University of Texas Southwestern Medical Center, USA

[NOT AVAILABLE ON DEMAND] *PNPLA3's Role in NAFLD*

**Hashem B. El-Serag**, Baylor College of Medicine, USA  
*Changing Epidemiological Trends in Non-Alcoholic Fatty Liver Disease versus Viral-Associated Hepatobiliary Cancers*

#### Non-Alcoholic Fatty Liver Disease, Liver Inflammation and Fibrogenesis in the Pathogenesis of Hepatobiliary Cancers (Joint) (9:10am Denver/Mountain Time Start)

\***Jay D. Horton**, University of Texas Southwestern Medical Center, USA

Session Chair

\***Alphonse E. Sirica**, Virginia Commonwealth University, USA

Session Chair

**Lopa Mishra**, George Washington University, USA  
*A TGF- $\beta$ -ALDH2 Axis in Obesity, Metabolic Syndrome, and HCC*

**Maria Rescigno**, Humanitas University, Italy  
*The Gut-Liver Axis in Liver Cancer Risk Conditions*

**Daniel A. Heller**, Memorial Sloan Kettering Cancer Center, USA  
*Lipid Dysregulation in Inflammation, NASH, and Cancer*

**Juan R. Sanabria**, Marshall University/Case Western Reserve University, USA  
*Short Talk: The  $\alpha$ 1-Na/K-ATPase/Src-p/PI3K Pathway Modulates the Survivin-SMAC Apoptotic "Switch" in NASH Related Hepatocellular Carcinoma: A Translational Study*

#### Career Roundtable (Joint) (12:30pm Denver/Mountain Time Start)

**Kendra K. Bence**, Pfizer Inc., USA

**Augusto Villanueva Rodriguez**, Icahn School of Medicine at Mount Sinai, USA

**Xin Wei Wang**, NCI, National Institutes of Health, USA

#### Poster Session 1 (Joint) (2pm Denver/Mountain Time Start)

#### Genetics of NAFLD (3pm Denver/Mountain Time Start) (EK28)

\***Jay D. Horton**, University of Texas Southwestern Medical Center, USA

Session Chair

\***Henry N. Ginsberg**, Columbia University Vagelos College of Physicians and Surgeons, USA

Session Chair

**Elizabeth K. Speliotes**, University of Michigan, USA  
*Use of GWAS to Identify SNPs Associated with NAFLD*

**Noura S. Abul-Husn**, Icahn School of Medicine at Mount Sinai, USA  
*Genomics and Liver Disease in Diverse Populations: From Biobanks to Patients*

**Karthickeyan Chella Krishnan**, University of Cincinnati, USA  
*Short Talk: Mouse and Human Population Studies Revealed Sex-Specific Roles of Liver Pyruvate Kinase in Promoting NAFLD/NASH*

**Mohammad Kabbani**, Rockefeller University, USA  
*Short Talk: Human Hepatocyte PNPLA3 148M Exacerbates Rapid Non-Alcoholic Fatty Liver Disease Development in Chimeric Mice*

**Ester Dohnalkova**, Mayo Clinic, USA  
*Short Talk: Hepatocyte-Specific Deletion of ROCK1 Prevents Liver Inflammation and Fibrosis in Murine Nonalcoholic Steatohepatitis*

**Neil A. Youngson**, Institute of Hepatology, UK  
*Short Talk: Acetyl-CoA Metabolism Drives Epigenome Change in Steatosis Leading to Widespread Abnormal Transcription and DNA Damage*

#### Tumor Microenvironment and Hepatobiliary Cancers (3pm Denver/Mountain Time Start) (EK29)

\***Lopa Mishra**, George Washington University, USA

Session Chair

**Silvia Affo**, Columbia University, USA  
*Role of Cancer Associated Fibroblasts in Cholangiocarcinoma*

**Amaia Lujambio**, Icahn School of Medicine at Mount Sinai, USA  
*Mechanisms of Immune Escape in Hepatocellular Carcinoma*

**Alphonse E. Sirica**, Virginia Commonwealth University, USA  
*The Desmoplastic Reaction and Intrahepatic Cholangiocarcinoma Progression: CAFs, Select Molecular Drivers, and Prognostic Implications*

\***Gregory J. Gores**, Mayo Clinic, USA  
*Targeting the Tumor Microenvironment for Cholangiocarcinoma Therapy*

**Yuhua Xue**, University of Pittsburgh, USA  
*Short Talk: p-Ezrin (Thr567) Synergizes with Akt Signaling to Accelerate Yap Mediated Cholangiocarcinogenesis but Correlates with a Favorable Prognosis in Human Intrahepatic Cholangiocarcinoma (ICC) Patient*

**Wen-Xing Ding**, University of Kansas Medical Center, USA  
*Short Talk: SQSTM1/p62 Inhibits whereas Nrf2 Promotes Tumorigenesis by Inducing Cell Population Remodeling and Metabolic Reprogramming in Mouse Livers with mTORC1 Activation and Defective Autophagy*

**Haichuan Wang**, University of California, San Francisco, USA  
*Short Talk: Requirement of Hippo Signaling Cascade during AXIN1 Mutation Driven Hepatocarcinogenesis*

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**Juan Pablo Unfried**, Weizmann Institute of Science, Israel  
*Short Talk: Long Non-Coding RNA NIHCOLE Promotes the DNA Damage Repair of Hepatocellular Carcinoma Cells*

### NAFLD and CVD (5:10pm Denver/Mountain Time Start) (EK28)

\***Henry N. Ginsberg**, Columbia University Vagelos College of Physicians and Surgeons, USA  
*The AAA Atase Torsin A, a New, Potent Player in VLDL Secretion, NAFL, and NASH*

\***Jay D. Horton**, University of Texas Southwestern Medical Center, USA  
*Molecular Mediators of NAFLD and Hyperlipidemia*

### TUESDAY, MARCH 23

#### Role of Lipids in NAFLD (8am Denver/Mountain Time Start) (EK28)

**Mitchell A. Lazar**, Perelman School of Medicine, University of Pennsylvania, USA  
*Circadian Contributions to NAFLD*

\***Catherine Postic**, INSERM Institut Cochin, France  
*Altered Insulin Signaling and Glucose Toxicity in NAFLD*

\***Hannele Yki-Järvinen**, University of Helsinki, Finland  
*Effects of Genetic Risk Factors for NAFLD on Hepatic Lipid Metabolism*

**Eran Elinav**, Weizmann Institute of Science, Israel  
*Host Microbiome Interactions in Health and Disease*

**HongMin Ni**, University of Kansas Medical Center, USA  
*Short Talk: Lack of VMP1 Impairs Hepatic Lipoprotein Secretion and Promotes Nonalcoholic Steatohepatitis in Mice*

**Joanne Hsieh**, Columbia University, USA  
*Short Talk: Sexually Dimorphic Mechanisms of Action of TTC39B in Hepatic Lipogenic Gene Expression*

**Xiao-Wei Chen**, Peking University, China  
*Short Talk: An ER Lipid Scramblase (ELS) Safeguards Lipoprotein Biogenesis and Lipid Homeostasis*

**Zhaoyue Zhang**, Princeton University, USA  
*Short Talk: Serine Catabolism Generates NADPH to Support Hepatic Lipogenesis*

#### Hepatobiliary Cancer Biomarkers and Molecular Subtypes (8am Denver/Mountain Time Start) (EK29)

\***Gregory J. Gores**, Mayo Clinic, USA  
*Session Chair*

\***Alphonse E. Sirica**, Virginia Commonwealth University, USA  
*Session Chair*

**Yujin Hoshida**, University of Texas Southwestern Medical Center, USA

*Liver Cancer Risk-Predictive Molecular Biomarkers Specific to Clinico-Epidemiological Contexts*

**Augusto Villanueva Rodriguez**, Icahn School of Medicine at Mount Sinai, USA

*Liquid Biopsy in Hepatobiliary Cancers*

**Jessica Zucman-Rossi**, University Paris Descartes-HEGP, France  
*Mechanisms of Liver Carcinogenesis Define Specific Molecular and Phenotypic HCC Subgroups*

**Jesper Bøje Andersen**, University of Copenhagen, Denmark  
*Defining Distinct Subtypes of Intrahepatic Cholangiocarcinoma by Molecular Profiling: Diagnostic, Prognostic, and Therapeutic Applications*

**Robert F. Schwabe**, Columbia University, USA  
*Discovery of Subgroup-Specific HCC Master Regulators by Systems Biology Approaches*

**Kerstin Seidel**, Genentech, USA

*Short Talk: Notch Inhibition Regresses Progenitor-Like HCCs by Inducing Hepatocyte Differentiation through Controlling C/EBP $\alpha$  Expression and HNF4 $\alpha$  Activity*

**Sungjin Ko**, University of Pittsburgh, USA  
*Short Talk: NOTCH-YAP1/TEAD-DNMT1 Axis Drives Hepatocyte Reprogramming into Intrahepatic Cholangiocarcinoma*

#### Meet the Editors (Joint) (12:30pm Denver/Mountain Time Start)

**Elena Bellafante**, Med - Cell Press, UK

**Francesco Giovinazzo**, Frontiers Journals, Italy

**Xin (Cindy) Sun**, Journal of Experimental Medicine at Rockefeller University Press, USA

#### Poster Session 2 (Joint) (2pm Denver/Mountain Time Start)

#### Pathways to NASH (3pm Denver/Mountain Time Start) (EK28)

\***Morris J. Birnbaum**, Pfizer Inc., USA  
*Session Chair*

**Mark A. McNiven**, Mayo Clinic, USA  
*Lipid Droplet Formation and Lipophagy in Fatty Liver Disease*

\***Tobias Walther**, Harvard/HHMI, USA  
*Lipid Droplet Biology in NAFLD*

**Annelise Poss**, University of Utah, USA

*Short Talk: Ceramides as Mediators of Endoplasmic Reticulum Stress in NASH*

**Cholsoon Jang**, University of California, Irvine, USA

*Short Talk: The Small Intestine Shields the Liver from Fructose-Induced Steatosis*

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**Kahealani Uehara**, University of Pennsylvania, USA

*Short Talk: Activation of Hepatic mTORC1 Protects Against NASH via Dual Regulation of VLDL- TAG Secretion and De Novo Lipogenesis*

**Sabine Daemen**, Washington University in St. Louis, USA

*Short Talk: The Hepatic Crown-like Structure in NASH: A Nexus between Monocyte-Derived Macrophages, Hepatic Stellate Cells, and Tissue Fibrosis*

**Samar Ibrahim**, Mayo Clinic, USA

*Short Talk: Lipid-Induced Endothelial Vascular Cell Adhesion Molecule 1 Promotes Nonalcoholic Steatohepatitis Pathogenesis*

**Wenke Jonas**, German Institute of Human Nutrition, Germany

*Short Talk: Immunity-Related GTPase IFGGA2 Induces Degradation of Hepatic Lipids by Lipophagy*

### Genomics, Molecular Heterogeneity, and Precision Medicine in Hepatobiliary Cancers (3pm Denver/Mountain Time Start) (EK29)

\***Lopa Mishra**, George Washington University, USA

*Session Chair*

\***Alphonse E. Sirica**, Virginia Commonwealth University, USA

*Session Chair*

**Irene Oi Lin Ng**, University of Hong Kong, Hong Kong

*Molecular Biomarkers in Hepatocellular Carcinoma*

**Xin Wei Wang**, NCI, National Institutes of Health, USA

*Causes and Functional Intricacies of Intertumor and Intratumor Heterogeneity in Primary Hepatobiliary Cancers*

**Renumathy Dhanasekaran**, Stanford University, USA

*Implications of Genetic Heterogeneity in Hepatocellular Carcinoma (HCC)*

**Teh Bin Tean**, Duke-NUS Medical School, Singapore

*Genomic and Epigenomic Studies of Cholangiocarcinoma and their Clinical Implications*

**Josep Llovet**, Icahn School of Medicine at Mount Sinai, USA

*Immune Therapies for HCC: is NASH-HCC Responding Different*

**Bangyan Stiles**, University of Southern California, USA

*Short Talk: Heterogeneous Liver Cancer Development Promoted by PTEN Regulated beta-Catenin and SOX9 Signal*

**Chungui Xu**, National Cancer Center/National Clinical Research

Center for Cancer/Cancer Hospi, China

*Short Talk: Gender Distinct in Genomic Features of HBV-Related Hepatocellular Carcinoma*

### WEDNESDAY, MARCH 24

#### Emerging Therapies for NASH (8am Denver/Mountain Time Start) (EK28)

\***Hannele Yki-Järvinen**, University of Helsinki, Finland

*Session Chair*

\***Morris J. Birnbaum**, Pfizer Inc., USA

*DGAT2 Inhibition for NASH*

**Chuhan Chung**, Gilead Sciences, USA

*Combination Therapies for NASH Cirrhosis*

**Greg Steinberg**, McMaster University, Canada

*Role of ATP Citrate Lyase (ACLY) in NASH and HCC*

**Kendra K. Bence**, Pfizer Inc., USA

*Inhibition of Fructose Metabolism for the Treatment of NAFLD*

**Lei Ling**, NGM Biopharmaceuticals, USA

*Therapeutic FGF19 in Non-Alcoholic Steatohepatitis*

**Aimee L. Edinger**, University of California, Irvine, USA

*Short Talk: A Drug-Like Sphingolipid Opposes Mitochondrial Fragmentation and Corrects the Metabolic Sequelae of Obesity*

**Brian Rady**, Janssen R&D, USA

*Short Talk: Inhibition of Hepatocyte Inflammasome Improves Features of NASH in foz/foz Mice*

**Haresh Sajiir**, University of Queensland - Mater Research Institute, Australia

*Short Talk: Development of Liver-Targeted Interleukin-22 for Fatty Liver Disease*

**Madhulika Tripathi**, Duke-NUS Medical School Singapore, Singapore

*Short Talk: HHcy is a Feature and Mediator of NASH that Permits B12 and Folate to be an Effective Therapy for NASH*

#### Advances in Molecular and Immune Targeting of Hepatobiliary Cancers (8am Denver/Mountain Time Start) (EK29)

\***Gregory J. Gores**, Mayo Clinic, USA

*Session Chair*

\***Lopa Mishra**, George Washington University, USA

*Session Chair*

**Tim F. Greten**, NCI, National Institutes of Health, USA

*Immunotherapies for Hepatobiliary Cancers: Current Status and Future Perspectives*

**R. Kate Kelley**, University of California, San Francisco, USA

*Developing Clinical Trials of Novel Therapeutic Agents and Treatment Combinations for Intrahepatic Cholangiocarcinoma*

**Bruno Sangro**, Clinica Universidad de Navarra, Spain

*Targeted Agent and Immune-Based Therapies for Hepatocellular Carcinoma*

**Miryam Müller**, CRUK Beatson Institute, UK

*Short Talk: Identifying Effective Subtype-Specific Treatment Responses in Hepatocellular Carcinoma in Genetically Engineered Mouse Models*

**Jonathan M. Hernandez**, NCI, National Institutes of Health, USA

*Short Talk: A Cytosolic Complex Between the Nuclear Export Protein XPO7 and Sterile 20-like Kinase (SLK) Drives Cholangiocarcinoma, and Reveals a Translatable Therapeutic Target*

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**Massimiliano Cadamuro**, University of Padua, Italy

*Short Talk: Inhibition of YAP Activation Induces Cell Senescence and Autophagy while Blocking Cell Proliferation in Cholangiocarcinoma (CCA)*

**Man Hsin Cindy Hung**, NCI, National Institutes of Health, USA

*Short Talk: Tumor Methionine Metabolism Drives T-Cell Exhaustion in Hepatocellular Carcinoma*

**Andreas Prokesch**, Medical University Graz, Austria

*Short Talk: Overcoming HCC Drug Resistance by Targeting Metabolic Flexibility Conferred by p53*

**Closing Remarks (10:50am Denver/Mountain Time Start) (EK28)**

**Closing Remarks (Organizers) (10:55am Denver/Mountain Time Start) (EK29)**

**Networking Lounge (Joint) (11am Denver/Mountain Time Start)**