10th

Korea-Japan-Taiwan
HBV RESEARCH SYMPOSIUM

April 27-28, 2024

Biomedical Research Institute, Seoul National Univ. Hospital, Seoul, Korea

KASL JSH TASL

Viral Hepatitis Study Group
Hepatitis Virus Study Group

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Dear colleagues and friends,

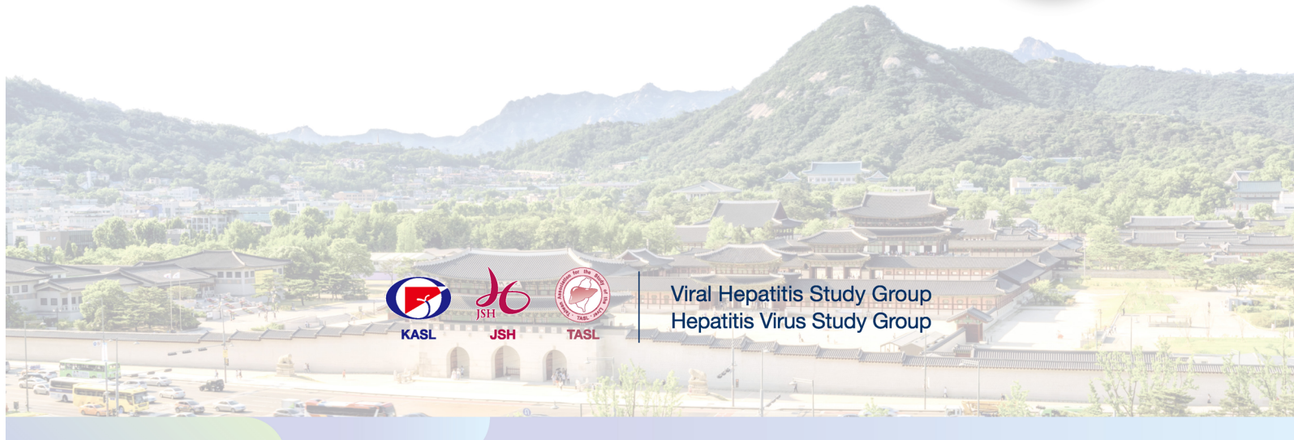
I am very happy to have an opportunity to invite our leading colleagues to the 10th Korea-Japan-Taiwan HBV Research Symposium in Seoul, April 27-28, 2024.

On behalf of the organizing committee, we heartily welcome the HBV researchers from Taiwan, Japan, and Korea to share the cutting-edge progress in your research and stimulate the spirit of collaboration for the advancement of our understanding of our formidable, yet intriguing foe.

Since the birth of this meeting in 2013 under the outstanding leadership of founding scholars, the HBV Research Symposium has greatly contributed to the academic friendship of the participants. This year, we are deeply grateful for being able to hold the first HBV Research Symposium in Korea. I look forward to meeting all our dear friends, both old and new, in the vibrant city of Seoul.

With deep gratitude,

Jin-Wook Kim
Congress President
10th Korea-Japan-Taiwan HBV Research Symposium
Seoul National University, Korea



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Biomedical Research Institute, Seoul National Univ. Hospital, Seoul, Korea

10th Korea-Japan-Taiwan HBV Research Symposium Organizing Committee

Congress President

Jin-Wook Kim, Korea

Chairman of Organizing Committee

Hyung Joon Yim, Korea
Kyun-Hwan Kim, Korea
Yasuhito Tanaka, Japan
Chun-Jen Liu, Taiwan
Sang Hoon Ahn, Korea

Director of Local Executive Committee

Secretary General: Hyun Woong Lee
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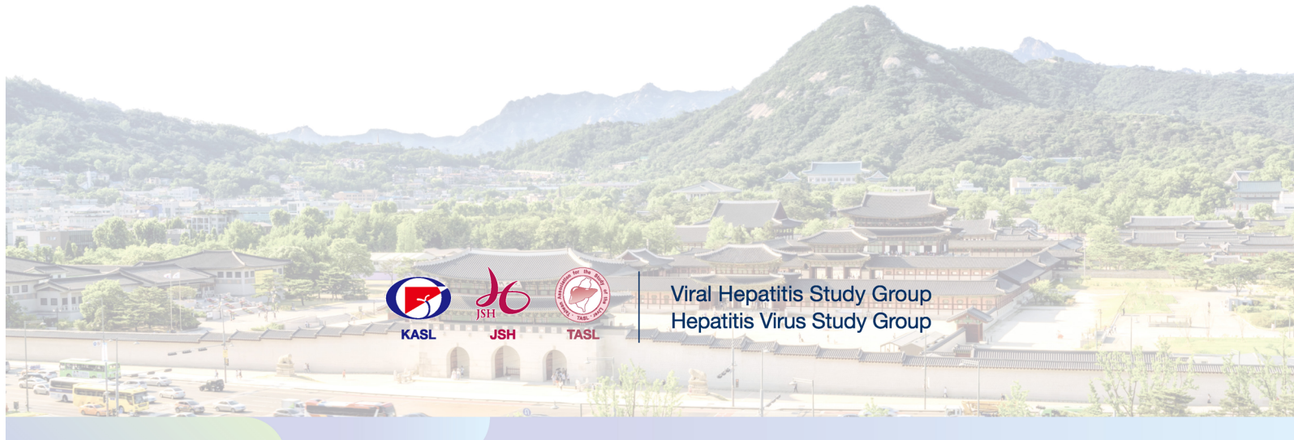
Scientific Director: Eui-Cheol Shin
Research Director: Eileen Laurel Yoon
Project Director: Won Seok Kang
Treasurer: Sun Young Yim
Public Relation: Sung Won Lee, Han Ah Lee



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HBV RESEARCH SYMPOSIUM

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Biomedical Research Institute, Seoul National Univ. Hospital, Seoul, Korea

Program at a Glance

Saturday, April 27, 2024

08:30-09:00	Registration
09:00-09:25	Opening
09:25-10:25	Session 1 **HBV Integration and HBx**
10:25-10:50	Coffee Break
10:50-12:20	Session 2 **Preclinical Targets and Therapies for Chronic Hepatitis B**
12:20-13:00	Lunch
13:00-13:30	Poster Viewing
13:30-13:55	**Special Lecture I**
13:55-15:25	Session 3 **Clinical View**
15:25-15:50	Coffee Break
15:50-16:15	**Special Lecture II**
16:15-17:45	Session 4 **Molecular Virology**
18:30-20:30	Dinner

Sunday, April 28, 2024

08:30-09:00	Registration
09:00-10:30	Session 5 **Immunology**
10:30-10:40	Closing

10th Korea-Japan-Taiwan

HBV RESEARCH SYMPOSIUM

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Biomedical Research Institute, Seoul National Univ. Hospital, Seoul, Korea

Saturday, April 27, 2024

08:30-09:00	Registration	
09:00-09:10	Opening Remarks	*Jin-Wook Kim (Korea), Hyung Joon Yim (Korea)*
09:10-09:25	Welcome Remarks	*Yasuhito Tanaka (Japan), Chun-Jen Liu (Taiwan), Sang Hoon Ahn (Korea)*
09:25-10:25	**Session 1. HBV Integration and HBx**	*Pei-Jer Chen (Taiwan), Jin-Wook Kim (Korea)*
09:25-09:40	HBx Mutations Developed during Antiviral Therapy	*Chau-Ting Yeh (Taiwan)* ··· 28
09:40-09:55	HBV DNA Integration Provides a DNA Biomarker for Subgrouping HBV-Driven HCC and Monitoring Residual HCC after Curative Therapies	*Shiou-Hwei Yeh (Taiwan)* ··· 30
09:55-10:10	The Role of N6-methyladenosine (m6A) RNA Methylation in the Hepatitis B Virus Life Cycle	*Geon-Woo Kim (Korea)* ··· 32
10:10-10:25	The Structural Study of the HBV x Protein (HBx)	*Shinichi Machida (Japan)* ··· 34
10:25-10:50	Coffee Break	
10:50-12:20	**Session 2. Preclinical Targets and Therapies for Chronic Hepatitis B**	*Yasuhito Tanaka (Japan), Kyun-Hwan Kim (Korea)*
10:50-11:05	Targeting KIF4 as a Novel Anti-HBV Entry Inhibitor	*Abdulla A. Mahmoud (Japan)* ··· 40
11:05-11:20	Identification of Novel Compounds as Potent Inhibitors of HBV Entry by Modeling-Based Fitting of NTCP Empty Pockets	*Kyun-Hwan Kim (Korea)* ··· 42
11:20-11:35	A Small Molecule iCDM-34 Identified by in Silico Screening Suppresses HBV DNA through Activation of Aryl Hydrocarbon Receptor	*Yutaka Furutani (Japan)* ··· 44
11:35-11:50	Targeting Capsid-Forming Ability of HBV Core Protein with Small-Molecule Inhibitors	*Chunkyu Ko (Korea)* ··· 46
11:50-12:05	The Role of an Innovative Therapeutics SAG-524 in HBV-RNA Destabilization	*Yasuhito Tanaka (Japan)* ··· 48
12:05-12:20	Sirtuin 2 Inhibitors Suppress HBV Replication	*Kyongmin Kim (Korea)* ··· 50
12:20-13:00	Lunch	
13:00-13:30	Poster Viewing	
13:30-13:55	**Special Lecture I**	*Sang Hoon Ahn (Korea)*
	Clinical Role and Significance of Glycan in HBV Infection	*Masashi Mizokami (Japan)* ··· 56

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Saturday, April 27, 2024

13:55-15:25	**Session 3. Clinical View**	*Chun-Jen Liu (Taiwan), Hyung Jun Yim (Korea)*
13:55-14:10	Using GAAD Score for Prediction of the Development of HCC in HBV-Related Cirrhosis Patients	*Tung-Hung Su (Taiwan)* ··· 62
14:10-14:25	The Association with iTACT-HBcrAg and HCC Risk after HBsAg Seroprevalence	*Tetsuya Hosaka (Japan)* ··· 64
14:25-14:40	Enhancing Functional Cure: Retreating Off-Nuc Clinical Relapse with Pegylated Interferon	*Wen-Juei Jeng (Taiwan)* ··· 66
14:40-14:55	HBsAg Decline Related to Immune Checkpoint Inhibitors in Cancer Patients	*Yi-Hsiang Huang (Taiwan)* ··· 68
14:55-15:10	Changes of Lipid Loading Capacity of Lipoproteins in Chronic Hepatitis B Patients Switching from TDF to TAF	*Pin-Nan Cheng (Taiwan)* ··· 70
15:10-15:25	Recent Prevalence and Characteristics of Patients with Hepatitis Delta Virus in Japan	*Naoya Sakamoto (Japan)* ··· 72
15:25-15:50	Coffee Break	
15:50-16:15	**Special Lecture II**	*Masamichi Muramatsu (Japan)*
	Control of Hepatitis B: A Successful Example of Scientific, Medical and Public Communities	*Pei-Jer Chen (Taiwan)* ··· 78
16:15-17:45	**Session 4. Molecular Virology**	*Chau-Ting Yeh (Taiwan), Koichi Watashi (Japan)*
16:15-16:30	Tripartite Motif-Containing Protein 21 Regulates Hepatocyte Nuclear Factors, Thereby Contributes to IFN-γ-Induced Suppression of HBV	*Juhee Won (Korea)* ··· 84
16:30-16:45	Why Macaque-Derived NTCP Cannot Function as an HBV Receptor?	*Kaho Shionoya (Japan)* ··· 86
16:45-17:00	TRIM26 Supports HBV Replication by Preventing Core Protein from Proteasome-Dependent Degradation	*Yuki Nakaya (Japan)* ··· 88
17:00-17:15	Epitranscriptomic Cytidine Methylation of the Hepatitis B Viral RNA Packaging Signal Is Essential for Viral Reverse Transcription	*Kevin Tsai (Taiwan)* ··· 90
17:15-17:30	Alteration of Gene Expression after Entecavir and Pegylated Interferon Therapy in HBV-Infected Chimeric Mouse Liver	*Masataka Tsuge (Japan)* ··· 92
17:30-17:45	Examination of Lipid Nanoparticles Loading Ribonucleoprotein-Oligonucleotide Complexes for Genome Editing to Hepatitis B Virus Inhibition *in vitro* and *in vivo*	*Kyoko Tsukiyama-Kohara (Japan)* ··· 94
18:30-20:30	Dinner	Seoulgaon (Sejong Art Center)

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HBV RESEARCH SYMPOSIUM

April 27-28, 2024

Biomedical Research Institute, Seoul National Univ. Hospital, Seoul, Korea

Sunday, April 28, 2024

08:30-09:00	Registration	
09:00-10:30	**Session 5. Immunology**	*Masanori Isogawa (Japan), Eui-Cheol Shin (Korea)*
09:00-09:15	HBV-Specific Tissue-Resident Memory T Cells in Human HBV-Infected Liver Diseases	*Yang Cheng (Taiwan)* ··· 100
09:15-09:30	Liver Sinusoidal T Cells in Healthy and HBV-Infected Livers	*Eui-Cheol Shin (Korea)* ··· 102
09:30-09:45	Selection of Viral Escape Mutants by $CD8^+$ T Cells in HBeAg-Negative Chronic Hepatitis B Patients	*Hung-Chih Yang (Taiwan)* ··· 104
09:45-10:00	Direct Analysis of Human Hepatic Stellate Cells by Flow Cytometry	*Hideki Ueno (Japan)* ··· 106
10:00-10:15	Distinct NK-like Liver Sinusoidal $CD56^{hi}CD8^+CD161^-$ T Cells Expanded in Patient with HBV Infection	*June-Young Koh (Korea)* ··· 108
10:15-10:30	Strategic Direction: Alliance to Combating Vertical Transmission of Hepatitis B in Tanzania – Mobilizing Support from Asia to Africa	*Jin Yong Kim (Korea)* ··· 110
10:30-10:40	Closing Address	*Pei-Jer Chen (Taiwan), Jin-Wook Kim (Korea)*

Poster Exhibition

PE-01	Functional Region in preS1 for Forming a Stable Complex with NTCP	*Chisa Kobayashi (Japan)*	··· 114
PE-02	Inhibitory Activity of Sterol Derivatives against HBV Entry and Its Mechanism	*Atsuto Kusunoki (Japan)*	··· 115
PE-03	Development of a Novel Liver-Immune Organoid Model to Reproduce the HBV Infected Liver Microenvironment	*Daichi Akuzawa (Japan)*	··· 116
PE-04	Mapping of Amino Acid Region in NTCP Involved in the Interaction with HBV preS1	*Kayo Matsuzawa (Japan)*	··· 117
PE-05	Role of Lipid Droplet Accumulation in HBV-HCC Development	*Ryuta Ueda (Japan)*	··· 118
PE-06	Decreased Risk of Hepatocellular Carcinoma in Patients with Chronic Hepatitis B Treated with Besifovir	*Seong Hee Kang (Korea)*	··· 119
PE-07	Effects of Tenofovir Disoproxil Fumarate versus Tenofovir Alafenamide on Risk of Osteoporotic Fracture in Patients with Chronic Hepatitis B	*Eunju Kim (Korea)*	··· 121
PE-08	Strong Cross-Neutralizing Antibodies Induced by a Hybrid Large Hepatitis B Surface Protein Composed of Two Viral Genotypes C and D	*Takahiro Sanada (Japan)*	··· 122
PE-09	Impact of Alpha-Fetoprotein Expression on Interferon Pathways and VEGFA in Hepatocellular Carcinoma Microenvironment after Hepatitis C Virus Eradication	*Katsuya Nagaoka (Japan)*	··· 123

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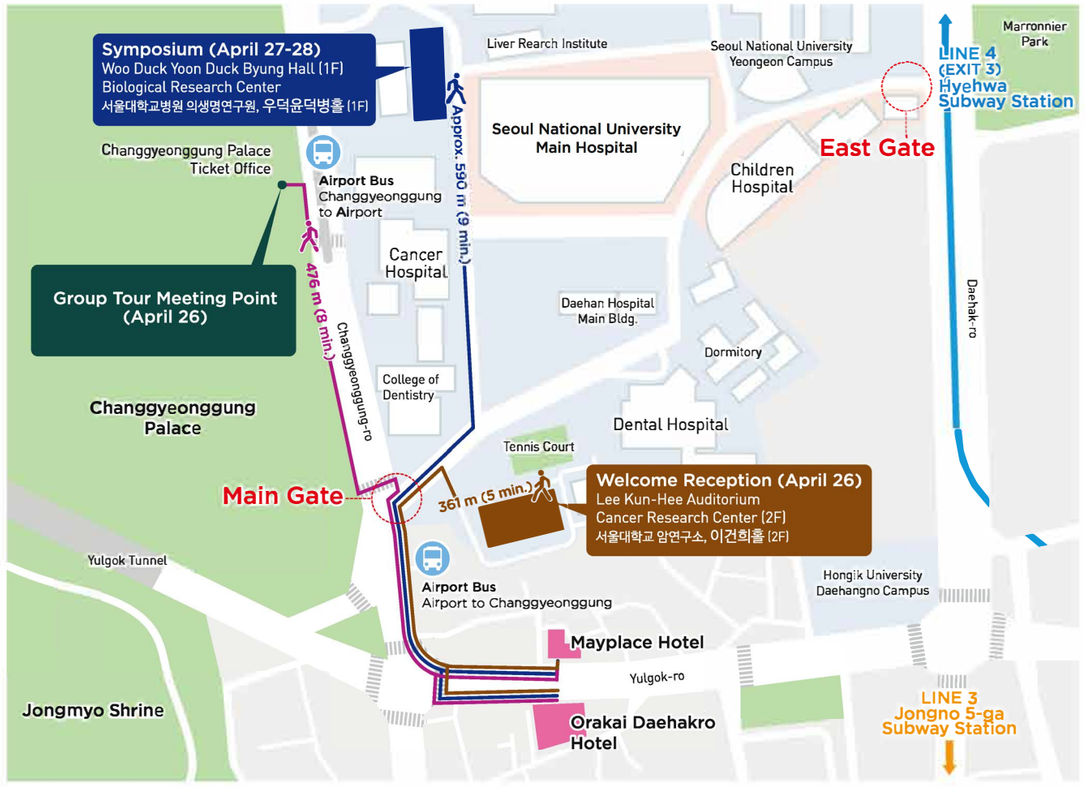


- **Group Tour (16:00, April 26, 2024)**
  Venue: Changgyeonggung Palace
  Please gather in front of the ticket office by 16:00 PM, and please do not purchase tickets. We will move together for the palace tour after we check attendance. After the tour, we will guide you to the welcome reception venue.

- **Welcome Reception (18:30, April 26, 2024)**
  Venue: Lee Kun-Hee Auditorium (2F), Cancer Research Institute, Seoul National University Hospital

- **Symposium Venue (April 27-28, 2024)**
  Venue: Woo Duck Yoon Duck Byung Hall (1F), Biomedical Research Institute, Seoul National University Hospital

- **Main Dinner-Social Hour (18:30, April 27, 2024)**
  Venue: Seoulgaon (Sejong Art Center)
  We will provide transportation for all participants to the dinner venue. Please utilize the provided coach service (round trip).

Group Photos from

The 9th Japan-Taiwan-Korea

HBV RESEARCH SYMPOSIUM

March 31 - April 2, 2023 Kumamoto City, Japan

Day 1. Saturday, April 27, 2024
Woo Duck Yoon Duck Byung Hall, Biomedical Research Institute, Seoul National Univ. Hospital

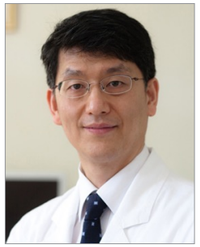
Opening Remarks

Jin-Wook Kim (Korea)
Hyung Joon Yim (Korea)

10th Korea-Japan-Taiwan HBV Research Symposium

Opening Remarks

Jin-Wook Kim



EDUCATION

1983-1989 (M.D.) Seoul National University (SNU) College of Medicine, Seoul, Korea: graduated *magna cum laude*

1991-1993 (M.S.) medical science, SNU Graduate School of Medicine, Seoul, Korea

1998-1999 (Ph.D.) medical science, SNU Graduate School of Medicine, Seoul, Korea

FELLOWSHIP and RESIDENCY TRAINING

Internship: SNU Hospital (1989-1990)

Residency (internal medicine): SNU Hospital (1990-1994)

Fellow, Infectious Diseases Section (Prof K. W. Choe), Department of internal Medicine, SNU Hospital (1997-98).

Fellow, Gastroenterology Section (Prof. Y.B. Yoon), Department of Internal Medicine, SNU Hospital (Seoul) (1998-99).

ACADEMIC APPOINTMENTS

Instructor, Department of Internal Medicine, Eulji University School of Medicine (1999-2000)

Associate professor, Department of Medicine, Seoul National University College of Medicine (2010-2023)

Professor, Department of Medicine, Seoul National University College of Medicine (2023-)

Research Interests

His research interests encompass mechanisms of transcriptional control of hepatitis B virus (HBV) replication, prognostication of chronic hepatitis B and prediction of HBV-associated hepatocellular carcinoma. Their team has shown characteristic roles of alcohol, small RNAs and methylation on the transcription of HBV cccDNA.

Publications

1. Park GC, Chung JW, Jang ES and **J-W Kim**. Association between adverse outcomes of hepatitis A and acetaminophen use: a population-based cohort study. Digestive and Liver Disease 2023, S1590-8658(23)00529-7.
2. Lee K, Choi GH, Jang ES, Jeong S-H and **J-W Kim**. A scoring system for predicting hepatocellular carcinoma risk in alcoholic cirrhosis. Sci Rep. 2022;12(1):1717.
3. Euh W, Lim S, **J-W Kim**. Sodium-Glucose Cotransporter-2 Inhibitors Ameliorate Liver Enzyme Abnormalities in Korean Patients with Type 2 Diabetes Mellitus and Nonalcoholic Fatty Liver Disease. Front Endocrinol 2021;12:613389.
4. Moon IY, **J-W Kim**. Methylation profile of hepatitis B virus is not influenced by interferon α in human liver cancer cells. Mol Med Rep. 2021;24(4):715.

10th Korea-Japan-Taiwan HBV Research Symposium

Opening Remarks

Hyung Joon Yim

Dr. Yim graduated from Korea University Medical College in 1994. He received internship, residency, and fellowship training at Korea University Medical Center. He also had research fellowship training periods in 2005-2006 at University of Michigan, Ann Arbor, MI, USA under the supervisor, Dr. Anna Lok. He earned Ph.D. degree at Korea University Graduate School from Dr. Kwan Soo Byun.

June 2017-Present	Korea Univ. Ansan Hospital, Director of Health Promotion Center
March 2017-Present	Korea Univ. Ansan Hospital, Director of Department of Internal Medicine
February 2016-February 2018	Korea Univ. Ansan Hospital, Chief of Division of Gastroenterolgy and Hepatology
February 2014-June 2015	National Institute of Health, Bethesda, MD, USA, Visiting Professor
March 2006-Present	Korea Univ. Ansan Hospital, Professor of Gastroenterolgy and Hepatology

Research Interests

Dr. Yim's research interests are viral hepatitis, complication of portal hypertension, alcoholic liver diseases, and hepatocellular carcinoma. Initially he focused on management of antiviral resistant chronic hepatitis B and then broadened to wide spectrum of chronic liver diseases such as chronic hepatitis C, hepatic fibrosis, and liver cancer.

Publications

1. **Yim HJ,** Kim W, Ahn SH, Yang JM, Jang JY, Kweon YO, Cho YK, Kim YJ, Hong GY, Kim DJ, Jung YK, Um SH, Sohn JH, Lee JW, Park SJ, Lee BS, Kim JH, Kim HS, Yoon SK, Kim MY, Lee KS, Lim YS, Lee WS, Han KH. Besifovir Dipivoxil Maleate 144-Week Treatment of Chronic Hepatitis B: An Open-Label Extensional Study of a Phase 3 Trial. Am J Gastroenterol. 2020 May 1
2. Lee HA, Kim SU, Seo YS, Lee YS, Kang SH, Jung YK, Kim MY, Kim JH, Kim SG, Suk KT, Jung SW, Jang JY, An H, **Yim HJ**, Um SH. Prediction of the varices needing treatment with non-invasive tests in patients with compensated advanced chronic liver disease. Liver Int. 2019 Jun;39(6):1071-1079.
3. Lee DW, **Yim HJ**, Seo YS, Na SK, Kim SY, Suh SJ, Hyun JJ, Jung SW, Jung YK, Koo JS, Kim JH, Yeon JE, Lee SW, Byun KS, Um SH. Prognostic assessment using a new substaging system for Barcelona clinic liver cancer stage C hepatocellular carcinoma: A nationwide study. Liver Int. 2019 Jun;39(6):1109-1119.
4. **Yim HJ**, Suh SJ, Jung YK, Yim SY, Seo YS, Lee YR, Park SY, Jang JY, Kim YS, Kim HS, Kim BI, Um SH. Daily Norfloxacin vs. Weekly Ciprofloxacin to Prevent Spontaneous Bacterial Peritonitis: A Randomized Controlled Trial. Am J Gastroenterol. 2018 Aug;113(8):1167-1176
5. Jung YK, **Yim HJ**. Reversal of liver cirrhosis: current evidence and expectations. Korean J Intern Med. 2017 Mar;32(2):213-228

Day 1. Saturday, April 27, 2024
Woo Duck Yoon Duck Byung Hall, Biomedical Research Institute, Seoul National Univ. Hospital

Welcome Remarks

Yasuhito Tanaka (Japan)
Chun-Jen Liu (Taiwan)
Sang Hoon Ahn (Korea)

10th Korea–Japan–Taiwan HBV Research Symposium

Welcome Remarks

Yasuhito Tanaka

2001-2002 Assistant professor at Department of Clinical Molecular Informative Medicine, Nagoya City University Graduate School of Medical Sciences
2002-2006 Lecturer at Department of Clinical Molecular Informative Medicine, Nagoya City University Graduate School of Medical Sciences
2006-2009 Associate professor at Department of Clinical Molecular Informative Medicine, Nagoya City University Graduate School of Medical Sciences
2009-2020 Professor and Director, Department of Virology & Liver unit, Nagoya City University Graduate School of Medical Sciences. Director, Liver Disease Unit, Nagoya City University Hospital
2020- Professor, Department of Gastroenterology and Hepatology, Kumamoto University; Vice Dean, Faculty of Life Science, Deputy Hospital Director and Director, Liver Center, Director, Endoscopy Center, Kumamoto University Hospital

Professor Tanaka has been working as a Gastroenterologist (Hepatologist) since 1991, and treated many patients with chronic viral hepatitis. They continue to do several molecular evolutionary analyses using human samples and collaborate with several researchers outside Japan, i.e. molecular clock study of HCV (ref. 1) worked with Dr. Harvey J Alter who won the Nobel Prize and recently finding unique HBV core mutations associated with HCC development in Alaskan Natives (ref. 2).
Since 2007, he became a representative of a National Project about GWAS, and we discovered IL28B SNPs associated with the response to PEG-IFN (ref. 3) and ITPA SNP. Until now, they have conducted Omics analyses such as epigenetic, RNAseq and microRNA using more than 8,000 samples, as well as gut dysbiosis. Most recently, genome-wide association study identified a TLL1 variant associated with development of HCC after eradication of HCV (ref. 4). They also focus drug screening for developing HBV therapeutics and optimization of the hit compounds (ref. 5) on the basis of another National Project (AMED). In clinical practice, their prospective observation study evidenced that monthly monitoring of HBV markers is useful for preventing HBV reactivation-related hepatitis among patients with resolved HBV infection following chemotherapies (ref. 6,7), and they made Japanese guideline to prevent HBV reactivation by HBV-DNA monitoring. Based on their clinical and basic knowledge, he is well-suited for his role in the project described in several grant applications.

Publications

Original Articles Total 470 (Total IF 3,667.7, citation 19,949, H-index 67 (2024)). 19 awarded.

1. **Tanaka Y**, Hanada K, Alter HJ. et al. **Proc Natl Acad Sci U S A**. 2002.99(24):15584-15589.
2. Hayashi S., McMahon BJ, **Tanaka Y(Corresponding)**, et al. **Hepatology**. 2019 ,69,19 -33.
3. **Tanaka Y**, Nishida N, Sugiyama M, et al. **Nature Genetics** 2009 41(10):1105-1109.
4. Matsuura K, **Tanaka Y (Corresponding)** et al. **Gastroenterology**. 2017 152(6):1383-1394.
5. Watanabe T, **Tanaka Y (Corresponding)**, et al. **J Gastroenterol**. 2024.
6. Kusumoto S, **Tanaka Y (equal contribution)**, et al. **J Hepatol**. 2020;73.285-293.
7. Inoue T, Kusumoto S, **Tanaka Y (Corresponding)**, et al. **J Hepatol**. 2021, 75(2):302 – 310.

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Welcome Remarks — Chun-Jen Liu

Chun-Jen LIU is a Professor at the Department of Internal Medicine, National Taiwan University College of Medicine. He achieved his MD and PhD at the National Taiwan University. He is currently Director of the Hepatitis Research Center, Director of Gastroenterology and Hepatology, and Director of Clinical Trial Center, National Taiwan University Hospital. He ever delivered the JGH Foundation Emerging Leader Lecture in APDW 2013. Recently, he received NTUH outstanding Research Award. He is now the President of the Taiwan Association for the Study of the Liver. He is also the associate editor, the Journal of the Formosan Medical Association, and Journal of Microbiology, Immunology and Infection. He has authored 380 papers in international, peer-reviewed journals.

Research Interests

Hepatitis B, Hepatitis C, HCC, and Steatotic liver disease

Publications

1. Liu CJ, Chen PJ, Lai MY, Kao JH, Chang CF, Wu HL, Shau WY, Chen DS. A prospective study characterizing full-length hepatitis B virus genomes during acute exacerbation. Gastroenterology 2003;124:80-90.
2. Liu CJ, Lo SC, Kao JH, Tseng PT, Lai MY, Ni YH, Yeh SH, Chen PJ, Chen DS. Transmission of occult hepatitis B virus by transfusion to adult and pediatric recipients in Taiwan. J Hepatol 2006;44:39-46.
3. Liu CJ, Lee PH, Lin DY, et al. Heparanase inhibitor PI-88 as adjuvant therapy for hepatocellular carcinoma after curative resection: A randomized phase II trial for safety and dose-finding. J Hepatol 2009;50:958-968.
4. Liu CJ, Chuang WL, Lee CM, et al. Peginterferon alfa-2a plus ribavirin for the treatment of dual chronic infection with hepatitis C and B viruses. Gastroenterology 2009;136:496-504.
5. Liu CJ, Chuang WL, Sheen IS, et al. Efficacy of ledipasvir and Sofosbuvir Treatment of HCV Infection in Patients Coinfected with HBV. Gastroenterology 2018;154:989-997.

10th Korea-Japan-Taiwan HBV Research Symposium

Welcome Remarks — Sang Hoon Ahn

Present Position:

Professor, Dept. of Internal Medicine, Yonsei Univ. College of Medicine, Seoul, Korea
Chief, Dept. of Gastroenterology and Hepatology, Severance Hospital, Yonsei Univ. College of Medicine, Seoul, Korea (2024-)
Director, Yonsei Gastroenterology Center, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea (2024-)
Director, Yonsei Liver Center, Severance Hospital, Yonsei Univ. College of Medicine, Seoul, Korea (2019-2023)
Director, Human Resources Headquaters, Yonsei Univ. Health System, Seoul, Korea (2021-2024)
Director, Administration of Yonsei Univ. Health System, Seoul, Korea (2020-2021)
Director, Planning and Management Headquarter, Severance Hospital, Yonsei Univ. Health System, Seoul, Korea (2018-2020)

Overseas Working Experiences:

2001-2003 Postdoctoral Fellowship, Liver Research Center, Brown Medical School, Providence, RI, USA
2008-2009 Visiting Professor, WHO Collaborating Centres for Virus Reference and Research, Victorian Infectious Diseases Reference Laboratory (VIDRL), Melbourne Health, North Melbourne, Australia

Key Academic Society Activities:

Trustee, Journal of Gastroenterology and Hepatology Foundation (JGHF) (2024-)
Executive Council Member, The Asian Pacific Association of the Study of the Liver (APASL) (2023-current)
Secretary-General, The Korean Association of the Study of the Liver (KASL) (2022-current)
Secretary General: The Korean Association of the Study of Liver (KASL, 2022-2023)
Chairman of Academic Committee: The Korean Liver Cancer Association (2010-2011)
Chairman of Academic Committee: The Asia-Pacific Primary Liver Cancer Expert Meeting (APPLE, 2013)
Chairman of Academic Committee: The Korean Association of the Study of Liver (KASL, 2018-2019)
Chairman of Academic Committee: The Asia Pacific Association of the Study of Liver (APASL, 2022)

Research Interests

- Viral hepatitis B and C: Molecular biology, Clinical trials for new drugs
- Liver fibrosis and liver cancer: Pathogenesis and treatment

Day 1. Saturday, April 27, 2024
Woo Duck Yoon Duck Byung Hall, Biomedical Research Institute, Seoul National Univ. Hospital

Session 1

HBV Integration and HBx

Pei-Jer Chen (Taiwan), Jin-Wook Kim (Korea)

HBx Mutations Developed during Antiviral Therapy
Chau-Ting Yeh (Taiwan)
HBV DNA Integration Provides a DNA Biomarker for Subgrouping HBV-Driven HCC and Monitoring Residual HCC after Curative Therapies
Shiou-Hwei Yeh (Taiwan)
The Role of N6-methyladenosine (m^6A) RNA Methylation in the Hepatitis B Virus Life Cycle
Geon-Woo Kim (Korea)
The Structural Study of the HBV x Protein (HBx)
Shinichi Machida (Japan)

• April 27, 2024 (Sat) 09:25-10:25 •

Introducing the Moderator — Pei-Jer Chen

Professor Chen was appointed Director of the Hepatitis Research Center at the National Taiwan University Hospital in Taipei in 2001-2003, and now the faculty for Graduate Institute of Clinical Medicine, National Taiwan University. He was the President of Taiwan Association for Study of the Liver (TASL) from 2012 to 2013. He served as the President of Taiwan Society of Virology from 2016-2018.

Research Interests

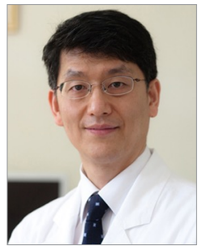
His research interests cover on the molecular virology and immunology of hepatitis viruses, and the genetic and genomic study of hepatocellular carcinoma. Professor Chen's clinical research include the natural history of chronic viral hepatitis and hepatocellular carcinoma, and also explores and conducts new therapies and trials for both diseases. He has published over 680 articles in the areas of hepatitis and hepatocellular carcinoma.

Publications

1. Chung CY, Sun CP, Tao MH, Wu HL, Wang SH, Yeh SH, Zheng QB, Yuan Q, Xia NS, Ogawa K, Nakashima K, Tetsuro S, **Chen PJ**: A Major HBV Spliced RNA Encoding one Novel Protein Important for Infection. J of Hepatology. 2024 Feb 7:S0168-8278(24)00116-8.
2. Yeh SH, Li CL, Lin YY, Ho MC, Wang YC, Tseng ST, **Chen PJ**: Hepatitis B Virus DNA Integration Drives Carcinogenesis and Provides a New Biomarker for HBV-related HCC. Cell Mol Gastroenterol Hepatol. 2023;15(4):921-929.
3. Li CL, Hsu CL, Lin YY, Ho MC, Hu RH, Chen CL, Ho TC, Lin YF, Tsai SF, Tzeng ST, Huang CF, Wang YC, Yeh SH, **Chen PJ**: HBV DNA Integration into Telomerase or MLL4 Genes and TERT Promoter Point Mutation as Three Independent Signatures in Subgrouping HBV-Related HCC with Distinct Features. Liver Cancer. 2023 Apr 17;13(1):41-55.
4. Chen CY, Chuang WL, Qin A, Zhang WH, Zhu LY, Zhang GQ, Chen JJ, Lo CC, Zhou X, Mao X, Shang J, Kuo HT, Xie W, Chen CH, Lo GH, Jun DW, Dang S, Tsai CY, Wang TF, Lai HH, Tseng KC, Huang YW, **Chen PJ**: A Phase 3 clinical trial validating the potency and safety of an innovative, extra-long-acting interferon in chronic hepatitis C. JGH Open. 2022 Oct 10;6(11):782-791.
5. Wu CR, Kim HJ, Sun CP, Chung CY, Lin YY, Tao MH, Kim JH, Chen DS, **Chen PJ**: Mapping the conformational epitope of a therapeutic monoclonal antibody against HBsAg by in vivo selection of HBV escape variants. Hepatology. 2022 Jul;76(1):207-219.

• April 27, 2024 (Sat) 09:25-10:25 •

Introducing the Moderator — Jin-Wook Kim



EDUCATION
1983-1989 (M.D.) Seoul National University (SNU) College of Medicine, Seoul, Korea: graduated *magna cum laude*
1991-1993 (M.S.) medical science, SNU Graduate School of Medicine, Seoul, Korea
1998-1999 (Ph.D.) medical science, SNU Graduate School of Medicine, Seoul, Korea
FELLOWSHIP and RESIDENCY TRAINING
Internship: SNU Hospital (1989-1990)
Residency (internal medicine): SNU Hospital (1990-1994)
Fellow, Infectious Diseases Section (Prof K. W. Choe), Department of internal Medicine, SNU Hospital (1997-98).
Fellow, Gastroenterology Section (Prof. Y.B. Yoon), Department of Internal Medicine, SNU Hospital (Seoul) (1998-99).
ACADEMIC APPOINTMENTS
Instructor, Department of Internal Medicine, Eulji University School of Medicine (1999-2000)
Associate professor, Department of Medicine, Seoul National University College of Medicine (2010-2023)
Professor, Department of Medicine, Seoul National University College of Medicine (2023-)

Research Interests

His research interests encompass mechanisms of transcriptional control of hepatitis B virus (HBV) replication, prognostication of chronic hepatitis B and prediction of HBV-associated hepatocellular carcinoma. Their team has shown characteristic roles of alcohol, small RNAs and methylation on the transcription of HBV cccDNA.

Publications

1. Park GC, Chung JW, Jang ES and **J-W Kim**. Association between adverse outcomes of hepatitis A and acetaminophen use: a population-based cohort study. Digestive and Liver Disease 2023, S1590-8658(23)00529-7.
2. Lee K, Choi GH, Jang ES, Jeong S-H and **J-W Kim**. A scoring system for predicting hepatocellular carcinoma risk in alcoholic cirrhosis. Sci Rep. 2022;12(1):1717.
3. Euh W, Lim S, **J-W Kim**. Sodium-Glucose Cotransporter-2 Inhibitors Ameliorate Liver Enzyme Abnormalities in Korean Patients with Type 2 Diabetes Mellitus and Nonalcoholic Fatty Liver Disease. Front Endocrinol 2021;12:613389.
4. Moon IY, **J-W Kim**. Methylation profile of hepatitis B virus is not influenced by interferon α in human liver cancer cells. Mol Med Rep. 2021;24(4):715.

• April 27, 2024 (Sat) 09:25-09:40 •

HBx Mutations Developed during Antiviral Therapy

Chau-Ting Yeh

Chang Gung Memorial Hospital, Taiwan

Recent studies indicated that HBx mutations could develop during Lamivudine and Entecavir antiviral therapies (Hepatol Int 2020). Further characterization showed that these mutants had a significant decrease of transactivation capabilities on pre-S1 promoter, leading to increased nuclear-to-cytoplasmic HBV core antigen and thus the cccDNA levels. On the other hand, another study identified new HBx mutations in post-entecavir treated HCC patients (Hepatology 2019). These HBx mutants had increased oncogenicity when co-expressed with the wild type whole HBV genome. We therefore focused on one of the HBx mutant, H94Y. It was found that H94Y mutant enhanced HBx protein stability in HCC cells. Inhibition of proteasome activities partially compromised the stability-enhancing effect, suggesting that proteasome activities is involved. Post-operative sample analysis showed that previous entecavir treatment (before HCC developed) was associated with higher frequency of H94Y mutation ($P = 0.049$ for H94Y singles mutation and $P = 0.003$ for H94Y/K130M double mutation; K130M is the basal-core-promoter-mutation correspondent HBx mutation). Development of this mutation was associated with higher HBx protein levels as well as poorer postoperative prognosis ($P < 0.001$, $P = 0.001$; and $P = 0.005$ for OS, recurrence free survival and metastasis-free survival). HBx nuclear localization was enhanced by this mutation together with increased cccDNA levels.

In summary, antiviral treatment could select HBx mutations. One of the entecavir-associated mutation, H94Y, could enhance HBx protein stability, which is partially dependent on protease activities. HBx-H94Y mutants increased HBx nuclear localization and cccDNA levels. Clinically, it was associated with unfavorable postoperative prognosis.

Introducing the Presenter — Chau-Ting Yeh

Chau-Ting Yeh received his MD degree from National Taiwan University, Medical School in 1984. He earned his PhD degree from Department of Molecular Microbiology and Immunology, USC, UA, in 1992.
Afterward, he went back to Taiwan to serve in Chang Gung Memorial Hospital and became the attending doctor in Department of hepato-gastroenterology in 1993. He had been appointed as the Director of Hepatology Division in Department of hepato-gastroenterology, Director of digestive core lab in Liver Research Unit, and Director of Liver Research Center in this hospital. He is now holding the position of Acting Director, Institute of stem cell and translational cancer research in Chang Gung Memorial hospital.

Research Interests

- Hepatitis viruses
- Hepatocarcinogenesis
- Anticancer treatments in hepatocellular carcinoma

Publications

Correspondence

1. Lai MW, Chang YL, Cheng PJ, Chueh HY, Chang SC, **Yeh CT***. Absence of chronicity in infants born to immunized mothers with occult HBV infection in Taiwan. J Hepatol. 2022 Jul;77(1):63-70.
2. Lin CL, Chu YD, **Yeh CT***. Emergence of Oncogenic-Enhancing Hepatitis B Virus X Gene Mutants in Patients Receiving Suboptimal Entecavir Treatment. Hepatology. 2019 May;69(5):2292-2296.
3. Lai MW, Lin TY, Tsao KC, Huang CG, Hsiao MJ, Liang KH, **Yeh CT***. Increased seroprevalence of HBV DNA with mutations in the s gene among individuals greater than 18 years old after complete vaccination. Gastroenterology. 2012 Aug;143(2):400-7.
4. **Yeh CT***, So M, Ng J, Yang HW, Chang ML, Lai MW, Chen TC, Lin CY, Yeh TS, Lee WC. Hepatitis B virus-DNA level and basal core promoter A1762T/G1764A mutation in liver tissue independently predict postoperative survival in hepatocellular carcinoma. Hepatology. 2010 Dec;52(6):1922-33.
5. Hsu CW, **Yeh CT***, Chang ML, Liaw YF. Identification of a hepatitis B virus S gene mutant in lamivudine-treated patients experiencing HBsAg seroclearance. Gastroenterology. 2007 Feb;132(2):543-50.

• April 27, 2024 (Sat) 09:40-09:55 •

HBV DNA Integration Provides a DNA Biomarker for Subgrouping HBV-Driven HCC and Monitoring Residual HCC after Curative Therapies

Shiou-Hwei Yeh, Chiao-Ling Li, Ming-Chih Ho, You-Yu Lin, Chia-Lang Hsu, Sheng-Tai Tzeng, Ya-Chun Wang, Pei-Jer Chen

National Taiwan University College of Medicine, Taipei, Taiwan; TCM Biotech International Corp., Taipei, Taiwan

HBV DNA integration occurs in less than 1% of infected hepatocytes but HBV DNA is present in the genome of ~90% of HBV-related HCCs. Whole genome sequencing showed integrations at random positions in chromosomes of CHB liver. However hotspot integrations in close to TERT and MLL4 genes were identified in the tumor, which occurs in a mutually exclusive manner and thus could help subgroup HBV-HCC with distinct features. It suggests a strong positive selection of HBV-integrated hepatocytes to drive the carcinogenic process and might shed new light on HBV-HCC biology. Besides, analysis of the integrated HBV DNA can help assess the possible time of HBV integration taking place and the influence of HBV genetic variants on carcinogenesis. Moreover, HBV integration in individual HCC generates a virus-host chimera DNA (vh-DNA) at junction site, presumably being a personalized circulating tumor DNA (ctDNA) biomarker for HBV-HCC. The clinical feasibility of vh-DNA as ctDNA biomarker for sensitive detection of residual tumors after tumor resection was not only demonstrated in our pilot study but also validated in a clinical trial completely recently. The results showed the presence of vh-DNA in post-operation plasma as an independent risk factor for predicting early HCC recurrence, with superior detection sensitivity, specificity, positive and negative predictive values than protein biomarkers. The ROC curve further supported a great achievement for the combination of vh-DNA with protein markers in predicting early recurrence. The use of vh-DNA to monitor residual tumors after other therapies currently in clinical use to assess prognosis, monitor recurrence, and guide adjuvant therapies is worthy of extensive testing.

Introducing the Presenter — Shiou-Hwei Yeh

Prof. Yeh received her Ph.D. degree at the Department of Molecular Medicine at the National Taiwan University College of Medicine. She is currently a Professor at the Department of Microbiology at National Taiwan University College of Medicine. Prof. Yeh has published more than 90 international scientific peer review papers in well regarded regarded journals. She has given more than 50 invited lectures in the area of her expertise on numerous occasions to international audiences. Her expertise is mainly the molecular mechanism of HBV related HCC.
She established several HCC animal models, with HCC derived from viral hepatitis, NAFLD, and stem cells, which were not only used for delineating the hepatocarcinogenic mechanisms but also used for testing the novel anti-tumor and anti-HBV drugs. She also has expertise in the molecular diagnosis, for hepatitis viruses and for HCC circulating biomarker development. She is also has expertise in basic virology of HBV, focusing on the nucleocapsid phosphorylation and viral morphogenesis. Her achievements won her several academic awards in Taiwan, including the National Science Council Outstanding Research Award, the Ministry of Science and Technology Outstanding Research Award, and honored as the Distinguished Professor at NTU.

Research Interests

- HBV integration in HCC: biomarker and therapeutic strategy development.
- Sex hormones in regulating the gender difference of HBV related HCC.
- Hepatic androgen receptor in liver metabolism and NAFLD pathogenesis.
- The mechanisms for hepatic stem cells to liver cancers.
- Drug development for targeted cancer therapy of HCC.
- Novel antiviral drug development, targeting to the phosphorylation of HBV nucleocapsid protein.

Publications

1. L1. Li CL, Li CY, Lin YY, Ho MC, Chen DS, Chen PJ, Yeh SH*. Androgen receptor enhances hepatic TERT transcription after Hepatitis B virus integration or somatic mutation in promoter region. Hepatology. 2019 Feb;69(2):498-512.
2. Li CL, Ho MC, Lin YY, Tzeng ST, Chen YJ, Pai HY, Wang YC, Chen CL, Lee YH, Chen DS, Yeh SH*, Chen PJ*. Cell-free virus-host chimera DNA from hepatitis B virus integration sites as a circulating biomarker of hepatocellular cancer. Hepatology. 2020;72(6):2063-2076.
3. Chen KW, Chen YS, Chen PJ, Yeh SH*. Androgen receptor functions in pericentral hepatocytes to decrease gluconeogenesis and avoid hyperglycemia and obesity in male mice. Metabolism. 2022;135:155269.
4. Yeh SH, Li CL, Lin YY, Ho MC, Wang YC, Tseng ST, Chen PJ*. Hepatitis B virus DNA integration drives carcinogenesis and provides a new biomarker for HBV-related HCC. Cell Mol Gastroenterol Hepatol. 2023 Jan 20:S2352-345X(23)00001-2.
5. Li CL, Hsu CL, Lin YY, Ho MC, Hu R, Chen CL, Lin YF, Tsai SF, Tzeng ST, Huang CF, Wang YC, Yeh SH*, Chen PJ*. HBV DNA integration into telomerase or MLL4 genes and TERT promoter point mutation as three independent signatures in subgrouping HBV-related HCC with distinct features. Liver Cancer 2023 Apr 17;13(1):41-55.

• April 27, 2024 (Sat) 09:55-10:10 •

The Role of N6-methyladenosine (m^6A) RNA Methylation in the Hepatitis B Virus Life Cycle

Geon-Woo Kim[1,3], Jae-Su Moon[2,3], and Aleem Siddiqui[3]

[1]Department of Microbiology and Molecular Biology, Chungnam National University, Daejeon, Korea,
[2]Center for Rare Disease Therapeutic Technology, Therapeutics & Biotechnology Division, Korea Research Institute of Chemical Technology (KRICT), Daejeon, Korea,
[3]Division of Infectious Diseases and Global Public Health, Department of Medicine, University of California, SanDiego, La Jolla, CA 92093, USA

N6-methyladenosine (m6A) RNA methylation most prevalently occurs in cellular and viral RNAs. Here, we investigated the m6A functions in the hepatitis B virus (HBV) life cycle. We identified a single m6A consensus motif at nucleotide position 1907. All HBV transcripts bear this motif at the 3′ end epsilon structure, but pregenome RNA (pgRNA) carries this motif twice, at 5′ and 3′ epsilon structures, owing to the terminal redundancy of sequences at its 5′ and 3′ end. Interestingly, m6A methylations differentially regulated the HBV life cycle dependent on its position. 3′ m6A modification reduced viral RNA stability, affecting corresponding viral protein expression, but 5′ m6A modification is essential for pgRNA encapsidation to synthesize viral DNA. Further, we found that HBV X (HBx) protein recruits host methyltransferases to nuclear HBV DNA to induce cotranscriptional m6A methylation. This study highlights the pivotal role of m6A methylation in the HBV life cycle.

Introducing the Presenter — Geon-Woo Kim

Experience

2022.09. Assistant Professor, Chungnam National University, Department of Microbiology and Molecular Biology, Daejeon, Korea
2022.02.-2022.08. Project Scientist, University of California, San Diego, Department of Medicine, La Jolla, USA
2018.09.-2022.02. Postdoctoral researcher, University of California, San Diego, Department of Medicine, La Jolla, USA
2018.01.-2018.08. Young scientist postdoctoral researcher, Korea Research Institute Chemical Technology and Korea Institute of Oriental Medicine, Daejeon, Korea
2016.09.-2017.12. Postdoctoral researcher, Department of Biotechnology, Yonsei University, Seoul, Korea

Education

2009.03.-2016.08. M.S. /Ph. D., Department of Biotechnology, Yonsei University, Seoul, Korea
2003.03.-2009.02. B.S., Department of Biotechnology, Sejong University, Seoul, Korea

Research Interests

Hepatitis B virus, Hepatitis C virus, Virus-host interaction

Publications

1. **Geon-Woo Kim**, Jae-Su Moon, Aleem Siddiqui. (2022) N6-methyladenosine modification of the 5' epsilon structure of the HBV pregenome RNA regulates its encapsidation by the viral core protein. Proc Natl Acad Sci U S A 15;119(7):e2120485119. PMID: 35135882.
2. **Geon-Woo Kim***, Jae-Su Moon, Aleem Siddiqui. (2022) N6-Methyladenine Modification of Hepatitis Delta Virus Regulates Its Virion Assembly by Recruiting YTHDF1. J Virol. 96 (19), e01124-22. PMID: 36102650.
3. **Geon-Woo Kim**, Aleem Siddiqui. (2021) N6-methyladenosine modification of HCV RNA genome regulates cap-independent IRES-mediated translation via YTHDC2 recognition. Proc Natl Acad Sci U S A 118(10);e2022024118. PMID: 33649237.
4. **Geon-Woo Kim**, Aleem Siddiqui. (2021) Hepatitis B virus X protein recruits methyltransferases to affect cotranscriptional N6-methyladenosine modification of viral/host RNAs. Proc Natl Acad Sci U S A 19;118(3):e2019455118. PMID: 33397803.
5. **Geon-Woo Kim**, Hasan Imam, Mohsin Khan, Saiful Anam Mir, Seong-Jun Kim, Seung Kew Yoon, Wonhee Hur, Aleem Siddiqui. (2021) HBV-Induced Increased N6-methyladenosine Modification of PTEN RNA Affects Innate Immunity and Contributes to HCC. Hepatology Doi:10.1002. PMID: 32394474.

• April 27, 2024 (Sat) 10:10-10:25 •

The Structural Study of the HBV x Protein (HBx)

Shinichi Machida

Department of Structural Virology, National Center for Global Health and Medicine, Japan

The global burden of Hepatitis B virus (HBV) infection is substantial, with an estimated 260 million chronic carriers worldwide and over 800,000 deaths annually due to complications such as cirrhosis and hepatocellular carcinoma (HCC). Current treatments, primarily based on nucleotide analog antiviral therapies, inhibit virus production but fail to cure the infection, as covalently closed circular DNA (cccDNA) remains in the nucleus of infected liver cells. Therefore, a definitive cure for chronic Hepatitis B should aim to eliminate or permanently silence cccDNA.

Transcription from cccDNA is regulated by the HBV x protein (HBx), which forms a complex with the host factor DDB1. This complex facilitates the proteasome-dependent degradation of the SMC5/6 complex, a repressor of cccDNA transcription. Notably, interventions targeting the HBx-DDB1 interaction have been shown to effectively restore Smc5/6 levels, leading to a decrease in viral protein and cccDNA levels. This mechanism not only promotes cccDNA transcription but also contributes to the development of HCC, partly through the inhibition of the DNA repair pathway.

However, due to the complexity of HBx as a poorly soluble protein, its structural and functional analysis has been challenging. To date, research has primarily provided peptide-level structural information regarding its interaction with DDB1, leaving the comprehensive structure of HBx largely unexplored. Furthermore, structural insights into its interaction with the SMC5/6 complex are lacking, representing a significant gap in our understanding of HBV pathogenesis and its implications for HCC development.

In this study, we elucidated the structure of HBx-DDB1 complexes at 2.98Å to uncover the structural foundation of HBV transcriptional regulation and HCC pathogenesis at the molecular level using Cryogenic Electron Microscopy (Cryo-EM) analysis.

Introducing the Presenter — Shinichi Machida

EDUCATION

2011-2014 Ph.D. in Science, Dept. of Electrical Engineering and Bioscience, Graduate School of Advanced Science and Engineering, Waseda Univ., Japan (Supervisor:Prof. Hitoshi Kurumizaka)

2008-2010 M.S. in Science, Dept. of Electrical Engineering and Bioscience, Graduate School of Advanced Science and Engineering, Waseda University, Japan

2004-2008 B.S. in Engineering, Dept. of Electrical Engineering and Bioscience, School of Advanced Science and Engineering, Waseda Univ., Japan

EXPERIENCE

2014-2017 Assistant professor in laboratory of Dr. Hitoshi Kurumizaka Dept. of Electrical Engineering and Bioscience, Graduate School of Advanced Science and Engineering, Waseda Univ., Japan

2017-2022 Postdoc in Molecular Virology Lab of Dr. Monsef Benkirane Institute of Human Genetics, Montpellier, France

2022-Current Director(tenure-track), Dept. of Structural Virology, National Center for Global Health and Medicine, Japan

Publications

1. Thenin-Houssier S, **Machida S (co-first author)**, Jahan C, Bonnet-Madin L, Abbou S, Chen HC, Tesfaye R, Cuvier O, Cuvier O, Benkirane M. POLE3 is a repressor of unintegrated linear HIV-1 DNA required for efficient virus integration and escape from innate immune sensing. **Science advances** 9, eadh3642 (2023)
2. Aoki M, Aoki-Ogata H, Bulut H, Hayashi H, Takamune N, Kishimoto N, Tanaka H, Higashi-Kuwata N, Hattori S, Das D, Venkateswara K, Iwama K, Davis D, Hasegawa K, Murayama K, Yarchoan R, Ghosh AK, Pau AK, **Machida S**, Misumi S, Mitsuya H. GRL-142 binds to and impairs HIV-1 integrase nuclear localization signal and potently suppresses highly INSTI-resistant HIV-1 variants. **Science advances** 9, eadg2955 (2023)
3. Wang W, Artiles KL, **Machida S**, Benkirane M, Jain M, Fire AZ. Combined direct/indirect detection allows identification of DNA termini in diverse sequencing datasets and supports a multiple-initiation-site model for HIV plus-strand synthesis BioRxiv, Preprint (2023)
4. **Machida S**, Diogo Dias J, Benkirane M. Faithful to the Marseille tradition: Unique and intriguing-that's how Marseillevirus packs its DNA. **Molecular Cell**, 82, 4401-4402 (2022)
5. **Machida S (co-corresponding)**, Depierre D, Chen HC, Thenin-Houssier S, Petitjean G, Doyen CM, Takaku M, Cuvier O, Benkirane M. Exploring histone loading on HIV DNA reveals a dynamic nucleosome positioning between unintegrated and integrated viral genome. **Proc Natl Acad Sci U S A**, 117, 6822-6830 (2020)

Day 1. Saturday, April 27, 2024
Woo Duck Yoon Duck Byung Hall, Biomedical Research Institute, Seoul National Univ. Hospital

Session 2

Preclinical Targets and Therapies for Chronic Hepatitis B

Yasuhito Tanaka (Japan), Kyun-Hwan Kim (Korea)

Targeting KIF4 as a Novel Anti-HBV Entry Inhibitor
Abdulla A. Mahmoud (Japan)
Identification of Novel Compounds as Potent Inhibitors of HBV Entry by Modeling-Based Fitting of NTCP Empty Pockets
Kyun-Hwan Kim (Korea)
A Small Molecule iCDM-34 Identified by in Silico Screening Suppresses HBV DNA through Activation of Aryl Hydrocarbon Receptor
Yutaka Furutani (Japan)
Targeting Capsid-Forming Ability of HBV Core Protein with Small-Molecule Inhibitors
Chunkyu Ko (Korea)
The Role of an Innovative Therapeutics SAG-524 in HBV-RNA Destabilization
Yasuhito Tanaka (Japan)
Sirtuin 2 Inhibitors Suppress HBV Replication
Kyongmin Kim (Korea)

• April 27, 2024 (Sat) 10:50-12:20 •

Introducing the Moderator

Yasuhito Tanaka

2001-2002 Assistant professor at Department of Clinical Molecular Informative Medicine, Nagoya City University Graduate School of Medical Sciences
2002-2006 Lecturer at Department of Clinical Molecular Informative Medicine, Nagoya City University Graduate School of Medical Sciences
2006-2009 Associate professor at Department of Clinical Molecular Informative Medicine, Nagoya City University Graduate School of Medical Sciences
2009-2020 Professor and Director, Department of Virology & Liver unit, Nagoya City University Graduate School of Medical Sciences. Director, Liver Disease Unit, Nagoya City University Hospital
2020- Professor, Department of Gastroenterology and Hepatology, Kumamoto University; Vice Dean, Faculty of Life Science, Deputy Hospital Director and Director, Liver Center, Director, Endoscopy Center, Kumamoto University Hospital

Professor Tanaka has been working as a Gastroenterologist (Hepatologist) since 1991, and treated many patients with chronic viral hepatitis. They continue to do several molecular evolutionary analyses using human samples and collaborate with several researchers outside Japan, i.e. molecular clock study of HCV (ref. 1) worked with Dr. Harvey J Alter who won the Nobel Prize and recently finding unique HBV core mutations associated with HCC development in Alaskan Natives (ref. 2).
Since 2007, he became a representative of a National Project about GWAS, and we discovered IL28B SNPs associated with the response to PEG-IFN (ref. 3) and ITPA SNP. Until now, they have conducted Omics analyses such as epigenetic, RNAseq and microRNA using more than 8,000 samples, as well as gut dysbiosis. Most recently, genome-wide association study identified a TLL1 variant associated with development of HCC after eradication of HCV (ref. 4). They also focus drug screening for developing HBV therapeutics and optimization of the hit compounds (ref. 5) on the basis of another National Project (AMED). In clinical practice, their prospective observation study evidenced that monthly monitoring of HBV markers is useful for preventing HBV reactivation-related hepatitis among patients with resolved HBV infection following chemotherapies (ref. 6,7), and they made Japanese guideline to prevent HBV reactivation by HBV-DNA monitoring. Based on their clinical and basic knowledge, he is well-suited for his role in the project described in several grant applications.

Publications

Original Articles Total 470 (Total IF 3,667.7, citation 19,949, H-index 67 (2024)). 19 awarded.

1. **Tanaka Y**, Hanada K, Alter HJ. et al. **Proc Natl Acad Sci U S A**. 2002.99(24):15584-15589.
2. Hayashi S., McMahon BJ, **Tanaka Y(Corresponding)**, et al. **Hepatology**. 2019 ,69,19 -33.
3. **Tanaka Y**, Nishida N, Sugiyama M, et al. **Nature Genetics** 2009 41(10):1105-1109.
4. Matsuura K, **Tanaka Y (Corresponding)** et al. **Gastroenterology**. 2017 152(6):1383-1394.
5. Watanabe T, **Tanaka Y (Corresponding)**, et al. **J Gastroenterol**. 2024.
6. Kusumoto S, **Tanaka Y (equal contribution)**, et al. **J Hepatol**. 2020;73.285-293.
7. Inoue T, Kusumoto S, **Tanaka Y (Corresponding)**, et al. **J Hepatol**. 2021, 75(2):302 – 310.

• April 27, 2024 (Sat) 10:50-12:20 •

Introducing the Moderator

Kyun-Hwan Kim

Kyun-Hwan Kim is a molecular virologist, currently a Professor of Precision Medicine at Sungkyunkwan University Medical School. He initially trained in Korea, obtaining a BS/MS from the Seoul National University and a Ph.D. at the Yonsei University, followed by postdoctoral studies at Brown University. He returned to Korea in 2005 to establish a Virology research laboratory at the Konkuk University in Seoul. He moved to Sungkyunkwan University in Mar 2020. He serves as an academic editor at PLoS ONE, Frontier in Immunology, and World Journal of Gastroenterology.

Research Interests

The Kyun-Hwan Kim's lab works in the fields of hepatitis B virus, influenza virus, corona virus, and virus-related diseases, attempting to decipher the molecular and cellular mechanisms that control viral replication, life-cycle, and virus-induced pathogenesis. Current interests and investigations include the viral evasion against host immune systems, drug resistance, and development of antivirals.

Publications

1. Shin GC, Lee MH, Kim N, et al., & **Kim KH***. Paraoxonase-2 agonist vutiglabridin promotes autophagy activation and mitochondrial function to alleviate non-alcoholic steatohepatitis. ***Br J Pharmacol. 2024***. In press.
2. Shin GC, Lee HM, Kim N, Seo SU, Kim KP, **Kim KH***. PRKCSH contributes to TNFSF resistance by extending IGF1R half-life and activation in lung cancer. ***Exp Mol Med. 2024*** Jan 10. doi: 10.1038/s12276-023-01147-1.
3. Shin GC, Moon SU, Kang HS, et al., & **Kim KH***. PRKCSH contributes to tumorigenesis by selective boosting of IRE1 signaling pathway. ***Nat. Commun. 2019***. Jul 18;10(1):3185.
4. Park ES, Byun YH, Park S, et al., & **Kim KH***. Co-degradation of interferon signaling factor DDX3 by PB1-F2 as a basis for high virulence of 1918 pandemic influenza. ***EMBO J. 2019***. Apr 12. pii: e99475.
5. Park ES, Lee AR, Kim DH, et al., & **Kim KH***. Identification of a quadruple mutation that confers tenofovir resistance in chronic hepatitis B patients. ***J Hepatol. 2019***. Feb 19. pii: S0168-8278(19)30120-5. Lee JH, **Kim KH***. Reply to the Response. ***J Hepatol. 2019*** Oct 1.

• April 27, 2024 (Sat) 10:50-11:05 •

Targeting KIF4 as a Novel Anti-HBV Entry Inhibitor

Sameh A. Gad, Abdulla A. Mahmoud, Hussein H. Aly

National Institute of Infectious Diseases, Japan

Recently, we identified pan-RXR agonist Bexarotene as an inhibitor of HBV/HDV infections through suppression of KIF4 cellular expression. However, Bexarotene has poor pharmacokinetic (PK) parameters and serious clinical side effects. Therefore, we looked for novel RXR agonists as potential anti-HBV entry inhibitors. Screening of different RXR agonists identified a new antiviral compound (RXR-X) which can efficiently block HBV (IC50 2.74 ± 0.82 μM and 2.05 ± 0.43 μM based on HBsAg and HBeAg, respectively) and HDV infections in PHH cultures. RXR-X anti-HBV effect was also verified by inhibition of HBV cccDNA, pregenomic RNA, and total intracellular HBV DNA. Compared to Bexarotene, RXR-X showed superior PK parameters and lower cytotoxicity. It also showed a modest inhibitory effect on NTCP bile uptake into PHH. Interestingly, it profoundly impeded HBV spread in long-term PHH cultures. Further analysis will be performed to identify the possible in-vivo effect of RXR-X.

Introducing the Presenter — Abdulla A. Mahmoud

Education and training

Visiting Graduate Student, The University of California San Diego, USA.
MSc. Biochemistry 2020, Faculty of Science, Helwan Univ., Egypt.
Bachelor of Science 2013, Faculty of Science, Helwan Univ., Egypt.

Work experience

Assistant Lecturer of Biochemistry, Faculty of Science, Helwan Univ., Egypt.
Demonstrator of Biochemistry, Faculty of Science, Helwan Univ., Egypt.

Research experience

Isolation of bioactive compounds from marine microorganisms.
Evaluation of their invitro anticancer, antiviral, and antibacterial activity.

Research Interests

- Molecular characterization of HBV/HDV virus-host interplay.
- Discovery of host factors that may have a role in HBV infection by gene silencing of the candidate host genes.
- Exploring novel anti-HBV drugs from deep sea Actinomycetes.

• April 27, 2024 (Sat) 11:05-11:20 •

Identification of Novel Compounds as Potent Inhibitors of HBV Entry by Modeling-Based Fitting of NTCP Empty Pockets

Nayeon Kim[1], Mehrangiz Dezhbord[1], Kyung-Soo Inn[2], Kyun-Hwan Kim[1,*]

[1]Department of Precision Medicine, Sungkyunkwan University School of Medicine, Suwon, Korea,
[2]Department of Life and Nanopharmaceutical Sciences, Kyung Hee University, Seoul, Korea

Hepatitis B virus (HBV) infection is a major global concern given its potential to cause liver cirrhosis and hepatocellular carcinoma. In order to prevent HBV infection at early steps, entry inhibitors have been tried to block the binding of virus to a NTCP receptor on the hepatocytes. While a number of HBV entry inhibitors have been identified, it is crucial to develop alternatives that effectively inhibit infection while minimizing adverse effects on the liver. Bile acids per se act as potential entry inhibitors, as they compete with virus particles for binding to NTCP. As the 3D structure of NTCP molecule was recently revealed, we utilized docking approach and investigated the fitting of bile acids and amino acid conjugated bile acids into the hydrophobic pockets of NTCP. A series of tested compounds consisting of amino acids and bile acids were highly effective in preventing HBV entry and infection in HepG2-NTCP cells. Treatment with bile acid-amino acid conjugates significantly impaired HBV entry in primary human hepatocytes (PHH) isolated from multiple independent donor patients. In HBV infected chimeric humanized liver mice, oral administration of the selected bile acid-amino acid conjugates inhibited the establishment of intrahepatic cccDNA and serum viral antigens. Preclinical pharmacokinetic profile showed promising results for drug development. Therefore, the bile acid-amino acid conjugates that was developed in this study holds potential as a novel orally administered compound that can impede HBV entry and restrict HBV infection.

Introducing the Presenter — Kyun-Hwan Kim

Kyun-Hwan Kim is a molecular virologist, currently a Professor of Precision Medicine at Sungkyunkwan University Medical School. He initially trained in Korea, obtaining a BS/MS from the Seoul National University and a Ph.D. at the Yonsei University, followed by postdoctoral studies at Brown University. He returned to Korea in 2005 to establish a Virology research laboratory at the Konkuk University in Seoul. He moved to Sungkyunkwan University in Mar 2020. He serves as an academic editor at PLoS ONE, Frontier in Immunology, and World Journal of Gastroenterology.

Research Interests

The Kyun-Hwan Kim's lab works in the fields of hepatitis B virus, influenza virus, corona virus, and virus-related diseases, attempting to decipher the molecular and cellular mechanisms that control viral replication, life-cycle, and virus-induced pathogenesis. Current interests and investigations include the viral evasion against host immune systems, drug resistance, and development of antivirals.

Publications

1. Shin GC, Lee MH, Kim N, et al., & Kim KH*. Paraoxonase-2 agonist vutiglabridin promotes autophagy activation and mitochondrial function to alleviate non-alcoholic steatohepatitis. ***Br J Pharmacol. 2024***. In press.
2. Shin GC, Lee HM, Kim N, Seo SU, Kim KP, Kim KH*. PRKCSH contributes to TNFSF resistance by extending IGF1R half-life and activation in lung cancer. ***Exp Mol Med. 2024*** Jan 10. doi: 10.1038/s12276-023-01147-1.
3. Shin GC, Moon SU, Kang HS, et al., & Kim KH*. PRKCSH contributes to tumorigenesis by selective boosting of IRE1 signaling pathway. ***Nat. Commun. 2019***. Jul 18;10(1):3185.
4. Park ES, Byun YH, Park S, et al., & Kim KH*. Co-degradation of interferon signaling factor DDX3 by PB1-F2 as a basis for high virulence of 1918 pandemic influenza. ***EMBO J. 2019***. Apr 12. pii: e99475.
5. Park ES, Lee AR, Kim DH, et al., & Kim KH*. Identification of a quadruple mutation that confers tenofovir resistance in chronic hepatitis B patients. ***J Hepatol. 2019***. Feb 19. pii: S0168-8278(19)30120-5. Lee JH, Kim KH*. Reply to the Response. ***J Hepatol. 2019*** Oct 1.

• April 27, 2024 (Sat) 11:20-11:35 •

A Small Molecule iCDM-34 Identified by in Silico Screening Suppresses HBV DNA through Activation of Aryl Hydrocarbon Receptor

Yutaka Furutani

Department of Laboratory Medicine, The Jikei University School of Medicine, Japan

Interferon (IFN)-alpha have been reported to suppress hepatitis B virus (HBV) cccDNA via APOBEC3 cytidine deaminase activity through interferon signaling. To develop a novel anti-HBV drug for a functional cure, we performed in silico screening of the binding compounds fitting the steric structure of the IFN-alpha-binding pocket in IFNAR2. We identified 37 compounds and named them in silico cccDNA modulator (iCDM)-1–37. We found that iCDM-34, a new small molecule with a pyrazole moiety, showed anti-HCV and anti-HBV activities. We measured the anti-HBV activity of iCDM-34 dependent on or independent of entecavir (ETV). iCDM-34 suppressed HBV DNA, pgRNA, HBsAg, and HBeAg, and also clearly exhibited additive inhibitory effects on the suppression of HBV DNA with ETV. We confirmed metabolic stability of iCDM-34 was stable in human liver microsomal fraction. Furthermore, anti-HBV activity in human hepatocyte-chimeric mice revealed that iCDM-34 was not effective as a single reagent, but when combined with ETV, it suppressed HBV DNA compared to ETV alone. Phosphoproteome and Western blotting analysis showed that iCDM-34 did not activate IFN-signaling. The transcriptome analysis of interferon-stimulated genes revealed no increase in expression, whereas downstream factors of aryl hydrocarbon receptor (AhR) showed increased levels of the expression. CDK1/2 and phospho-SAMHD1 levels decreased under iCDM-34 treatment. In addition, AhR knockdown inhibited anti-HCV activity of iCDM-34 in HCV replicon cells. These results suggest that iCDM-34 decreases the phosphorylation of SAMHD1 through CDK1/2 suppression, and reduces HCV replicon RNA, HBV DNA, and pgRNA formation under AhR activation.

Introducing the Presenter

Yutaka Furutani

1999-2001	Research fellow for young scientists, JSPS
2001	Ph. D. in Bioscience, Tokyo Institute of Technology, Japan
2001-2003	Researcher in ERATO Sekiguchi Extracellular Biosignaling Project, JST
2004-2005	Postdoctoral fellow in Molecular Cellular Pathology Research Unit, RIKEN
2005-2010	Research scientist in Laboratory for Neurobiology of Synapse, RIKEN Brain Science Institute
2010-2013	Staff scientist in Laboratory for Neurobiology of Synapse, RIKEN Brain Science Institute
2013-2018	Research scientist in Micro-signaling Regulation Technology Unit, RIKEN Center for Life Science Technologies
2018-2019	Senior scientist in Liver Cancer Prevention Research Unit, RIKEN Center for Medical Science
2019-2022	Senior scientist in Liver Cancer Prevention Research Unit, RIKEN Cluster of Pioneering Research
2022-Present	Lecturer in Department of Laboratory Medicine, The Jikei University School of Medicine

Publications

1. *Furutani Y. et al. A small molecule iCDM-34 identified by in silico screening suppresses HBV DNA through activation of aryl hydrocarbon receptor. Cell Death Discov. 2023 Dec 22;9(1):467.
2. Delobel D., Furutani Y., Nagoshi S., Tsubota A., Miyasaka A., Watashi K., Wakita T., Matsuura T., *Usui K. SEB Genotyping: SmartAmp-Eprimer Binary code Genotyping for complex, highly variable targets applied to HBV. BMC Infection Diseases, 2022, 22(1):516
3. Sakai M., Takahashi N., Ikeda H., Furutani Y., Higuchi S., Suzuki T., Dohmae N., Kobayashi S., Harada H., Kojima S., Matsuura T., Hattori A., *Kakeya H. Research for Design, synthesis, and target identification of new hypoxia-inducible factor 1 (HIF-1) inhibitors containing 1-alkyl-1H-pyrazole-3-carboxamide moiety. Bioorg Med Chem. 2021, 46(15): 116375
4. *Gailhouste L., Sudoh M., Watashi K., Wakita T., Ochiya T., Matsuura T., Kojima S., *Furutani Y. Research for Epigenetic reprogramming promotes the antiviral action of IFNα in HBV-infected cells. Cell Death Discovery. 2021, 7(1):130
5. *Furutani Y., Toguchi M., Shiozaki-Sato Y., Qin X.Y., Sudoh M., Suzuki H., Takahashi N., Kakeya H., Kojima S. Research for An interferon-like small chemical compound CDM-3008 suppresses hepatitis B virus through induction of interferon-stimulated genes. PLOS One, 2019, 14(6): e0216139

• April 27, 2024 (Sat) 11:35-11:50 •

Targeting Capsid-Forming Ability of HBV Core Protein with Small-Molecule Inhibitors

Chunkyu Ko

Korea Research Institute of Chemical Technology (KRICT), Korea

Chronic infection with the hepatitis B virus (HBV) affects approximately 296 million individuals globally, resulting in approximately 800,000 deaths annually. Individuals living with these viruses face a high risk of developing liver cirrhosis and liver cancer. While current nucleos(t)ide analogue therapy effectively controls HBV replication, it cannot eradicate the virus. Therefore, a comprehensive understanding of the life cycles of HBV is imperative to identify new antiviral targets and develop innovative therapeutics, ultimately aiming for the eradication of HBV infections. Capsid assembly modulators (CAMs) are small molecules that bind to HBV core proteins and modulate capsid assembly process, resulting in aberrant or HBV genome-free capsids. In this talk, antiviral potency and detailed mode-of-action of a new CAM will be introduced.

Introducing the Presenter — Chunkyu Ko

Dr. Chunkyu Ko received his Ph.D. (2015) from Yonsei University College of Science, Seoul, Republic of Korea, and his postdoctoral training (2015-2021) from Institute of Virology, Helmholtz Munich, Munich, Germany.
Then, he joined Infectious Diseases Therapeutics Research Center, Korea Research Institute of Chemical Technology (KRICT) in 2021, where he is currently working as a senior researcher.

Research Interests

- HBV and HDV infection cccDNA biogenesis
- Development of HBV/HDV models and antivirals

Publications

1. Kim H, **Ko C***, Lee JY, Kim M. 2021. Current Progress in the Development of Hepatitis B Virus Capsid Assembly Modulators: Chemical Structure, Mode-of-Action and Efficacy. Molecules 26(24):7420. * shared first authorship
2. **Ko C**, Su J, Festag J, Bester R, Kosinska AD, Protzer U. 2021. Intramolecular recombination enables the formation of hepatitis B virus (HBV) cccDNA in mice after HBV genome transfer using recombinant AAV vectors. Antiviral Res 194:105140.
3. **Ko C**, Bester R, Zhou X, Xu Z, Blossey C, Sacherl J, Vondran FWR, Gao L, Protzer U. 2019. A new role for capsid assembly modulators to target mature hepatitis B virus capsids and prevent virus Infection. Antimicrob Agents Chemother 64:e01440-01419.
4. **Ko C**, Chakraborty A, Chou WM, Hasreiter J, Wettengel JM, Stadler D, Bester R, Asen T, Zhang K, Wisskirchen K, McKeating JA, Ryu WS, Protzer U. 2018. Hepatitis B virus genome recycling and de novo secondary infection events maintain stable cccDNA levels. J Hepatol 69:1231-1241.
5. **Ko C**, Michler T, Protzer U. 2017. Novel viral and host targets to cure hepatitis B. Current opinion in virology 24:38-45.

• April 27, 2024 (Sat) 11:50-12:05 •

The Role of an Innovative Therapeutics SAG-524 in HBV-RNA Destabilization

Takehisa Watanabe[1], Sanao Hayashi[1], Katsuya Nagaoka[1], Yasuhito Tanaka[1]

[1]Department of Gastroenterology and Hepatology, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan

Background: Nucleos(t)ide analogues (NAs), currently used as approved drugs for HBV treatment, are excellent agents with potent activity against HBV-DNA but poor efficacy against HBs antigen (HBsAg). The effectiveness and tolerability of peginterferon also fall short of expectations. Therefore, this study aims to develop a novel drug with a novel mode of action (MoA) against HBV and good tolerability.

Methods: Based on drug screening from 30,000 library compounds using HepG2.2.15 cells and HBV-infected PXB cells, followed by the optimization, we obtained a SAG-524 compound with potent anti-HBsAg activity (IC50= 1.4 nM). The MoA of SAG-524 was evaluated by Northern blotting, BRIC assay, NRO assay. Then we used RNA interference to investigate the molecules that influence HBsAg expression. In vivo efficacy and safety were evaluated in animal models.

Results: SAG-524 treatments significantly reduced the stability of HBV-RNA in HepG2.2.15 cells without impacting GAPDH mRNA, indicating specific destabilization for HBV-RNA, while SAG-524 did not suppress transcription. The diminished effect of SAG-524 after PAPD5 knockdown suggested the involvement of PAPD5 in the MoA of SAG-524. ELAVL1, an RNA-binding protein recently identified as a potential anti-HBV drug target, suppresses HBsAg with or without SAG-524 treatment; however, this suppression is reversed by PAPD5 knockdown, indicating PAPD5's direct or indirect involvement in the effects of ELAVL1. The oral administration of SAG-524 in human liver chimeric mice demonstrated a reduction in HBsAg, and the combination with NAs resulted in significant decreases of both serum HBsAg and HBV-DNA, as well as cccDNA in liver. Safety evaluations in both mice and monkeys revealed no significant toxicity of the SAG-524.

Conclusion: The SAG-524 is an orally available and well-tolerated anti-HBV therapeutic agent that potently suppresses HBsAg. It has the potential to destabilize HBV-RNA and possibly induce functional cure in combination therapy with NA.

Introducing the Presenter — Yasuhito Tanaka

2001-2002 Assistant professor at Department of Clinical Molecular Informative Medicine, Nagoya City University Graduate School of Medical Sciences
2002-2006 Lecturer at Department of Clinical Molecular Informative Medicine, Nagoya City University Graduate School of Medical Sciences
2006-2009 Associate professor at Department of Clinical Molecular Informative Medicine, Nagoya City University Graduate School of Medical Sciences
2009-2020 Professor and Director, Department of Virology & Liver unit, Nagoya City University Graduate School of Medical Sciences. Director, Liver Disease Unit, Nagoya City University Hospital
2020- Professor, Department of Gastroenterology and Hepatology, Kumamoto University; Vice Dean, Faculty of Life Science, Deputy Hospital Director and Director, Liver Center, Director, Endoscopy Center, Kumamoto University Hospital

Professor Tanaka has been working as a Gastroenterologist (Hepatologist) since 1991, and treated many patients with chronic viral hepatitis. They continue to do several molecular evolutionary analyses using human samples and collaborate with several researchers outside Japan, i.e. molecular clock study of HCV (ref. 1) worked with Dr. Harvey J Alter who won the Nobel Prize and recently finding unique HBV core mutations associated with HCC development in Alaskan Natives (ref. 2). Since 2007, he became a representative of a National Project about GWAS, and we discovered IL28B SNPs associated with the response to PEG-IFN (ref. 3) and ITPA SNP. Until now, they have conducted Omics analyses such as epigenetic, RNAseq and microRNA using more than 8,000 samples, as well as gut dysbiosis. Most recently, genome-wide association study identified a TLL1 variant associated with development of HCC after eradication of HCV (ref. 4). They also focus drug screening for developing HBV therapeutics and optimization of the hit compounds (ref. 5) on the basis of another National Project (AMED). In clinical practice, their prospective observation study evidenced that monthly monitoring of HBV markers is useful for preventing HBV reactivation-related hepatitis among patients with resolved HBV infection following chemotherapies (ref. 6,7), and they made Japanese guideline to prevent HBV reactivation by HBV-DNA monitoring. Based on their clinical and basic knowledge, he is well-suited for his role in the project described in several grant applications.

Publications

Original Articles Total 470 (Total IF 3,667.7, citation 19,949, H-index 67 (2024)). 19 awarded.

1. Tanaka Y, Hanada K, Alter HJ. et al. **Proc Natl Acad Sci U S A**. 2002.99(24):15584-15589.
2. Hayashi S., McMahon BJ, Tanaka Y(Corresponding), et al. **Hepatology**. 2019 ,69,19 -33.
3. Tanaka Y, Nishida N, Sugiyama M, et al. **Nature Genetics** 2009 41(10):1105-1109.
4. Matsuura K, Tanaka Y (Corresponding) et al. **Gastroenterology**. 2017 152(6):1383-1394.
5. Watanabe T, Tanaka Y (Corresponding), et al. **J Gastroenterol**. 2024.
6. Kusumoto S, Tanaka Y (equal contribution), et al. **J Hepatol**. 2020;73.285-293.
7. Inoue T, Kusumoto S, Tanaka Y (Corresponding), et al. **J Hepatol**. 2021, 75(2):302 – 310.

• April 27, 2024 (Sat) 12:05-12:20 •

Sirtuin 2 Inhibitors Suppress HBV Replication

Jumi Kim[1,2], Hyeonjoong Kwon[1,2], Muhammad Azhar Sajjad[1,2], Chanho Song[1,2], Jiseon Ha[1,2], Jae Woo Park[1], Kyongmin Kim[1,2,*]

[1] Department of Microbiology, Ajou University School of Medicine, Suwon, Republic of Korea
[2] Department of Biomedical Science, Graduate School of Ajou University, Suwon, Republic of Korea

Previously we showed that AGK2, a known selective Sirtuin 2 (SIRT2) inhibitor, inhibit Hepatitis B virus (HBV) replication in HBV-transfected cells, possibly by downregulating AKT/GSK-3β/β-catenin signaling. In this study, we further explore the additional antiviral mechanism of AGK2 and the potential of targeting SIRT2 to inhibit HBV replication. As expected, elevated endogenous SIRT2 expression and the deacetylation of α-tubulin were observed in HBV-transfected and -infected cells, further strengthening a potential role of SIRT2 in viral replication. While some SIRT2 inhibitors inhibited HBV RNA and DNA syntheses, others inhibited HBV DNA synthesis without any significant changes in HBV RNA level. Notably, AGK2 treatment resulted in a pronounced decrease in covalently closed circular DNA (cccDNA), indicating that AGK2, as a multifaceted antiviral, on HBV life cycle. Further investigation by chromatin immunoprecipitation assay revealed that AGK2 reduced the recruitment of SIRT2 to cccDNA, accompanied by enhanced deposition of transcriptional repressive epigenetic markers. Additionally, AGK2 treatment resulted in decreased recruitment of RNA polymerase II and acetylated H3 to cccDNA, supporting transcriptional repression of HBV. In this study, we provide evidence that AGK2 inhibits HBV replication by epigenetic modification of cccDNA. SIRT2 inhibition may suggest novel therapeutic strategies for targeting HBV infections.

Introducing the Presenter — Kyongmin Kim

1981.03.01-1985.02.28. Bachelor's (BS), Yonsei University, Department of Biology, Seoul, KOREA
1985.09.01-1988.02.28. Master of Science (MS), Yonsei University, Graduate School, Seoul, KOREA
1991.09.01-1996.05.01. PhD Education, Univ. of Texas at Austin, Division of Biology, Molecular Virology, Austin, TX, USA (PhD in Division of Biology, 1996.05.) Dr. Shinji Makino
1996.09.-1999.10. Postdoctoral Fellow, California Institute of Technology, Pasadena, CA (Dr. James Strauss Lab)
2013.04.-2013.10. Sabbatical year (6 months)- University of Texas Medical Branch at Galveston, TX, USA (Dr. Shinji Makino Lab)

Research Interests

- Molecular biology of hepatitis B virus replication
- Host-hepatitis B virus interactions
- Antiviral researches (hepatitis B virus and coronavirus)

Publications

1. yeonjoong Kwon, Jumi Kim, Chanho Song, Muhammad Azhar Sajjad, Jiseon Ha, Jaesung Jung, Sun Park, Ho-Joon Shin, and **Kyongmin Kim***. Peptidyl-Prolyl cis/trans Isomerase Pin1 Interacts with Hepatitis B Virus Core Particle, But Not with HBc Protein, to Promote HBV Replication. **Front. Cell. Infect. Microbiol**. 2023, 13:1195063.
2. **Kyongmin Kim***. PPIases Par14/Par17 Affect HBV Replication in Multiple Ways. **Viruses** 2023: 15: 457.
3. Jumi Kim, Hyeonjoong Kwon, Fadia Kalsoom, Muhammad Azhar Sajjad, Hyun Woong Lee, Jin Hong Lim, Jaesung Jung, Yong-Joon Chwae , Sun Park, Ho-Joon Shin, and **Kyongmin Kim***. Ca2+/Calmodulin-Dependent Protein Kinase II Inhibits Hepatitis B Virus Replication from cccDNA via AMPK Activation and AKT/mTOR Suppression. **Microorganisms 2022**: 10: 498.
4. Umar Saeed, Zahra Zahid Piracha, Hyeonjoong Kwon, Jumi Kim, Fadia Kalsoom, Yong-Joon Chwae, Sun Park, Ho-Joon Shin, Hyun Woong Lee, Jin Hong Lim, and **Kyongmin Kim***. The HBV Core Protein and Core Particle Both Bind to the PPIase Par14 and Par17 to Enhance Their Stabilities and HBV Replication. **Front. Microbiol. 2021**: 12:795047.
5. Zahra Zahid Piracha, Umar Saeed, Jumi Kim, HyeonJoong Kwon, Yong-Joon Chwae, Hyun Woong Lee, Jin Hong Lim, Sun Park, Ho-Joon Shin, and **Kyongmin Kim***. An Alternatively Spliced Sirtuin 2 Isoform 5 Inhibits Hepatitis B Virus Replication from cccDNA by Repressing Epigenetic Modifications Made by histone lysine methyltransferases. **Journal of Virology 2020** 94:e00926-20.

Special Lecture I

Sang Hoon Ahn (Korea)

Clinical Role and Significance of Glycan in HBV Infection
Masashi Mizokami (Japan)

• April 27, 2024 (Sat) 13:30-13:55 •

Introducing the Moderator — Sang Hoon Ahn

Present Position:
Professor, Dept. of Internal Medicine, Yonsei Univ. College of Medicine, Seoul, Korea
Chief, Dept. of Gastroenterology and Hepatology, Severance Hospital, Yonsei Univ. College of Medicine, Seoul, Korea (2024-)
Director, Yonsei Gastroenterology Center, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea (2024-)
Director, Yonsei Liver Center, Severance Hospital, Yonsei Univ. College of Medicine, Seoul, Korea (2019-2023)
Director, Human Resources Headquaters, Yonsei Univ. Health System, Seoul, Korea (2021-2024)
Director, Administration of Yonsei Univ. Health System, Seoul, Korea (2020-2021)
Director, Planning and Management Headquarter, Severance Hospital, Yonsei Univ. Health System, Seoul, Korea (2018-2020)

Overseas Working Experiences:
2001-2003 Postdoctoral Fellowship, Liver Research Center, Brown Medical School, Providence, RI, USA
2008-2009 Visiting Professor, WHO Collaborating Centres for Virus Reference and Research, Victorian Infectious Diseases Reference Laboratory (VIDRL), Melbourne Health, North Melbourne, Australia

Key Academic Society Activities:
Trustee, Journal of Gastroenterology and Hepatology Foundation (JGHF) (2024-)
Executive Council Member, The Asian Pacific Association of the Study of the Liver (APASL) (2023-current)
Secretary-General, The Korean Association of the Study of the Liver (KASL) (2022-current)
Secretary General: The Korean Association of the Study of Liver (KASL, 2022-2023)
Chairman of Academic Committee: The Korean Liver Cancer Association (2010-2011)
Chairman of Academic Committee: The Asia-Pacific Primary Liver Cancer Expert Meeting (APPLE, 2013)
Chairman of Academic Committee: The Korean Association of the Study of Liver (KASL, 2018-2019)
Chairman of Academic Committee: The Asia Pacific Association of the Study of Liver (APASL, 2022)

Research Interests
- Viral hepatitis B and C: Molecular biology, Clinical trials for new drugs
- Liver fibrosis and liver cancer: Pathogenesis and treatment

• April 27, 2024 (Sat) 13:30-13:55 •

Clinical Role and Significance of Glycan in HBV Infection

Masashi Mizokami

Genome Medical Sciences Project, Research Institute, National Center for Globa Health and Medicine, Japan

Around 300 million are persistently infected with hepatitis B virus (HBV) worldwide. The HBV vaccine has already been developed as a preventive method, but it has been pointed out that the effect is insufficient. On the other hand, although humans have deciphered all of humanity's genetic information and obtained the "blueprint for humanity", we are also facing new challenges. Various phenomena that were previously thought to be explained by genetic information can no longer be explained. Therefore, glycans, which play an important role in the "post-translation" process, are currently attracting attention.

"Glycan" refers to a group of compounds in which various sugars are linked together in a chain through glycosidic bonds. Glycans are attached to every cell in the human. The main function of glycans is to facilitate communication between cells in the body. Glycans attached to cells act as antennas and maintain homeostasis. Furthermore, when a virus invades, glycans sense it and instruct other cells to attack the virus.

Many studies are currently being conducted on the relationship between HBV and glycans. Some of them are introduced below.

1. Adsorption of HBV particles to cells: It has been shown that glycans on the surface of hepatocytes aid in the adsorption of HBV particles to target cells and contribute to the entry of HBV particles into cells.
2. Virus proliferation and infectivity: The development and practical application of functional analysis technology for sugar chains and glycans genes has made it possible to analyze the glycan synthesis system and sugar chain-related genes necessary for the proliferation and secretion of HBV. This will lead to the development of therapeutic drugs.
3. Liver and glycans: The liver is an important organ in the study of sugar chains and glycans, and they have become clear that a characteristic of liver disease is that liver-derived glycoproteins change significantly as the disease progresses.

I will explain in detail the relationship with HBV and glycans.

Introducing the Presenter

1976 M.D., from Nagoya City University Medical School
1978-1981 Department of Gastroenterology Social Insurance Chukyo Hospital
1984-1987 Trainee as needed Under Dr, Gojobori T, National Institute of Genetics Japan
1988-1990 Liver Unit, King's College Hospital, Liver Unit as Clinical Research Fellow
1990 Ph.D. from Nagoya City University Medical School
2000-2001 Professor, Department of Laboratory Medicine, Nagoya City Univ. Medical School
2001-2001 Professor, Department of Molecular Informative Medicine and Liver Unit, Nagoya City University Graduate School of Medicine
2008-2016 Director General, Research Center for Hepatitis and Immunology, National Center for Global Health and Medicine
2016- Director, Genome Medical Sciences Project, Research Institute, National Center for Global Health and Medicine

Honours

- 1980 Research Award by Viral Hepatitis Research Foundation of Japan
- 2010 HAKONEYAMA Award by International Cooperation Medical Research Promotion Foundation
- 2011 Oda Award by Japan Society of Hepatology
- 2011 Okuda Memorial Award (Asian Pacific Digestive Week)
- 2012 Okuda Oration (Asian Pacific Association for the Study of the Liver)
- 2023 A life member of the Pontifical Academy of Sciences

Publications

My total publication 689, total citations 32,399, and H-index 82 from PubMed as of Dec 31, 2023.
15 typical papers are listed as below.

1. Orito E, **Mizokami M**, Ina Y, Moriyama EN, Kameshima N, Yamamoto M, T Gojobori T. Host-independent evolution and a genetic classification of the hepadnavirus family based on nucleotide sequences. **Proc Natl Acad Sci U S A**. 1989 86(18):7059-62.
2. Lau JY, **Mizokami M**, Ohno T, Diamond DA, Kniffen J, Davis GL. Discrepancy between biochemical and virological responses to interferon-alpha in chronic hepatitis C. **Lance**t. 1993 342(8881):1208-9.
3. **Mizokami M**, Gojobori T, and Lau JY. Molecular evolutionary virology: its application to hepatitis C virus. **Gastroenterology**. 1994 107(4):1181-2.
4. **Mizokami M**, Lau JY, Suzuki K, Nakano T, Gojyobori T. Different sensitivity of hepatitis C virus quasispecies to interferon-alpha therapy. **J Hepatol**. 1994 Nov;21(5):884-6.
5. Kudo T, Morishima T, Tszuki K, Orito E, **Mizokami M**. Hepatitis G virus in immunosuppressed padiatric allograft recipients. **Lancet**. 1996 Sep 14;348(9029 9:751.

Day 1. Saturday, April 27, 2024
Woo Duck Yoon Duck Byung Hall, Biomedical Research Institute, Seoul National Univ. Hospital

Session 3

Clinical View

Chun-Jen Liu (Taiwan), Hyung Jun Yim (Korea)

Using GAAD Score for Prediction of the Development of HCC in HBV-Related Cirrhosis Patients
Tung-Hung Su (Taiwan)

The Association with iTACT-HBcrAg and HCC Risk after HBsAg Seroprevalence
Tetsuya Hosaka (Japan)

Enhancing Functional Cure: Retreating Off-Nuc Clinical Relapse with Pegylated Interferon
Wen-Juei Jeng (Taiwan)

HBsAg Decline Related to Immune Checkpoint Inhibitors in Cancer Patients
Yi-Hsiang Huang (Taiwan)

Changes of Lipid Loading Capacity of Lipoproteins in Chronic Hepatitis B Patients Switching from TDF to TAF
Pin-Nan Cheng (Taiwan)

Recent Prevalence and Characteristics of Patients with Hepatitis Delta Virus in Japan
Naoya Sakamoto (Japan)

• April 27, 2024 (Sat) 13:55-15:25 •

Introducing the Moderator — Chun-Jen Liu

Chun-Jen LIU is a Professor at the Department of Internal Medicine, National Taiwan University College of Medicine. He achieved his MD and PhD at the National Taiwan University. He is currently Director of the Hepatitis Research Center, Director of Gastroenterology and Hepatology, and Director of Clinical Trial Center, National Taiwan University Hospital. He ever delivered the JGH Foundation Emerging Leader Lecture in APDW 2013. Recently, he received NTUH outstanding Research Award. He is now the President of the Taiwan Association for the Study of the Liver. He is also the associate editor, the Journal of the Formosan Medical Association, and Journal of Microbiology, Immunology and Infection. He has authored 380 papers in international, peer-reviewed journals.

Research Interests

Hepatitis B, Hepatitis C, HCC, and Steatotic liver disease

Publications

1. Liu CJ, Chen PJ, Lai MY, Kao JH, Chang CF, Wu HL, Shau WY, Chen DS. A prospective study characterizing full-length hepatitis B virus genomes during acute exacerbation. Gastroenterology 2003;124:80-90.
2. Liu CJ, Lo SC, Kao JH, Tseng PT, Lai MY, Ni YH, Yeh SH, Chen PJ, Chen DS. Transmission of occult hepatitis B virus by transfusion to adult and pediatric recipients in Taiwan. J Hepatol 2006;44:39-46.
3. Liu CJ, Lee PH, Lin DY, et al. Heparanase inhibitor PI-88 as adjuvant therapy for hepatocellular carcinoma after curative resection: A randomized phase II trial for safety and dose-finding. J Hepatol 2009;50:958-968.
4. Liu CJ, Chuang WL, Lee CM, et al. Peginterferon alfa-2a plus ribavirin for the treatment of dual chronic infection with hepatitis C and B viruses. Gastroenterology 2009;136:496-504.
5. Liu CJ, Chuang WL, Sheen IS, et al. Efficacy of ledipasvir and Sofosbuvir Treatment of HCV Infection in Patients Coinfected with HBV. Gastroenterology 2018;154:989-997.

• April 27, 2024 (Sat) 13:55-15:25 •

Introducing the Moderator — Hyung Joon Yim

Dr. Yim graduated from Korea University Medical College in 1994. He received internship, residency, and fellowship training at Korea University Medical Center. He also had research fellowship training periods in 2005-2006 at University of Michigan, Ann Arbor, MI, USA under the supervisor, Dr. Anna Lok. He earned Ph.D. degree at Korea University Graduate School from Dr. Kwan Soo Byun.

June 2017-Present	Korea Univ. Ansan Hospital, Director of Health Promotion Center
March 2017-Present	Korea Univ. Ansan Hospital, Director of Department of Internal Medicine
February 2016-February 2018	Korea Univ. Ansan Hospital, Chief of Division of Gastroenterolgy and Hepatology
February 2014-June 2015	National Institute of Health, Bethesda, MD, USA, Visiting Professor
March 2006-Present	Korea Univ. Ansan Hospital, Professor of Gastroenterolgy and Hepatology

Research Interests

Dr. Yim's research interests are viral hepatitis, complication of portal hypertension, alcoholic liver diseases, and hepatocellular carcinoma. Initially he focused on management of antiviral resistant chronic hepatitis B and then broadened to wide spectrum of chronic liver diseases such as chronic hepatitis C, hepatic fibrosis, and liver cancer.

Publications

1. Yim HJ, Kim W, Ahn SH, Yang JM, Jang JY, Kweon YO, Cho YK, Kim YJ, Hong GY, Kim DJ, Jung YK, Um SH, Sohn JH, Lee JW, Park SJ, Lee BS, Kim JH, Kim HS, Yoon SK, Kim MY, Lee KS, Lim YS, Lee WS, Han KH. Besifovir Dipivoxil Maleate 144-Week Treatment of Chronic Hepatitis B: An Open-Label Extensional Study of a Phase 3 Trial. Am J Gastroenterol. 2020 May 1
2. Lee HA, Kim SU, Seo YS, Lee YS, Kang SH, Jung YK, Kim MY, Kim JH, Kim SG, Suk KT, Jung SW, Jang JY, An H, Yim HJ, Um SH. Prediction of the varices needing treatment with non-invasive tests in patients with compensated advanced chronic liver disease. Liver Int. 2019 Jun;39(6):1071-1079.
3. Lee DW, Yim HJ, Seo YS, Na SK, Kim SY, Suh SJ, Hyun JJ, Jung SW, Jung YK, Koo JS, Kim JH, Yeon JE, Lee SW, Byun KS, Um SH. Prognostic assessment using a new substaging system for Barcelona clinic liver cancer stage C hepatocellular carcinoma: A nationwide study. Liver Int. 2019 Jun;39(6):1109-1119.
4. Yim HJ, Suh SJ, Jung YK, Yim SY, Seo YS, Lee YR, Park SY, Jang JY, Kim YS, Kim HS, Kim BI, Um SH. Daily Norfloxacin vs. Weekly Ciprofloxacin to Prevent Spontaneous Bacterial Peritonitis: A Randomized Controlled Trial. Am J Gastroenterol. 2018 Aug;113(8):1167-1176
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• April 27, 2024 (Sat) 13:55-14:10 •

Using GAAD Score for Prediction of the Development of HCC in HBV-Related Cirrhosis Patients

Tung-Hung Su

National Taiwan University Hospital, Taiwan

In CHB-related cirrhosis patients on long-term antiviral therapy, hepatocellular carcinoma (HCC) risk persists, motivating the need for risk stratification. The GAAD score, encompassing gender, age, alpha-fetoprotein, and des-gamma carboxyprothrombin (DCP) measurements, is designed for early-stage HCC detection. We would like to investigate the predictive role of the GAAD score in HCC development in CHB-related cirrhosis patients on antiviral therapy.

We conducted a retrospective cohort study to include HBV-related cirrhotic patients undergoing long-term antiviral therapy with regular HCC surveillance. The on-treatment plasma samples were retrieved for alpha-fetoprotein and DCP measurements by the Roche Elecsys® system to calculate the GAAD score. Cox proportional hazard regression analysis identified risk predictors for HCC.

A total of 499 patients were included and categorized into "prior HCC" (n=47), "HCC" (n=56), and "no HCC" (n=396) groups with a median GAAD score of 1.12, 0.84, and 0.54, respectively (p←0.001). Among the 452 patients without prior HCC, their median age was 60, and they received a median of 6.2 years of antiviral therapy. After a median of 3.3 years of follow-up, 56 patients developed HCC. A GAAD score of 0.71, and 1.64 significantly stratified the risk of HCC (logrank P←0.0001). After adjusting for age, sex, and FIB-4 index, a GAAD score →= 1.64, 0.71-1.64 significantly increased the risks of HCC by 8.68-fold (95% CI: 3.50-21.55) and 2.25-fold (0.96-5.25) compared with a GAAD score ← 0.71. We thus concluded that after 6 years of antiviral therapy, a high GAAD score significantly stratified the development of HCC and should receive intensive HCC surveillance.

Introducing the Presenter — Tung-Hung Su

Dr. Tung-Hung Su earned his M.D. degree from the National Taiwan University College of Medicine in 2001 and his Ph.D. from the Graduate Institute of Clinical Medicine at the same university in 2015. He has been an attending physician specializing in Hepatology and a Clinical Associate Professor in the Department of Internal Medicine at the National Taiwan University Hospital since 2020. From 2017 to 2019, he worked as a visiting scholar at Stanford University. Dr. Su's research focuses on translational research on treating liver fibrosis, managing viral hepatitis B and C, hepatocellular carcinoma, and using artificial intelligence models to study liver diseases. He has published several research papers in these fields.

Research Interests

- Viral hepatitis B
- Liver cirrhosis
- Hepatocellular carcinoma
- Artificial intelligence models for liver disease

Publications

1. Huang CT, Chu YL, **Su TH**, Huang SC, Tseng TC, Hsu SJ, Liao SH, Hong CM, Liu CH, Yang HC, Liu CJ, Chen PJ, Kao JH. Optimizing survival benefit by surgical resection by the seven-eleven criteria in Barcelona clinic liver cancer stage A/B hepatocellular carcinoma beyond the Milan criteria. Liver Cancer (2023) 12 (6): 539–549. (Co-corresponding author)
2. Huang SC, **Su TH**, Tseng TC, Chen CL, Hsu SJ, Liao SH, Hong CM, Liu CH, Lan TY, Yang HC, Liu CJ, Chen PJ, Kao JH. Distinct effects of hepatic steatosis and metabolic dysfunction on the risk of hepatocellular carcinoma in chronic hepatitis B. Hepatol Int. 2023 Oct;17(5):1139-1149. (Co-corresponding author)
3. Huang SC, **Su TH**, Tseng TC, Chen CL, Hsu SJ, Liu CH, Liao SH, Hong CM, Lan TY, Yang HC, Liu CJ, Chen PJ, Kao JH. Metabolic dysfunction-associated steatotic liver disease facilitates hepatitis B surface antigen seroclearance and seroconversion. Clinical Gastroenterology and Hepatology. 2023 Oct 21:S1542-3565(23)00842-X. (Co-corresponding author)
4. **Su TH**, Chang SH, Chen CL, Liao SH, Tseng TC, Hsu SJ, Hong CM, Liu CH, Yang HC, Liu CJ, Chen PJ, Kao JH. Serial increase and high alpha-fetoprotein levels predict the development of hepatocellular carcinoma in 6 months. Hepatol Res. 2023 Oct;53(10):1021-1030
5. **Su TH**, Wu CH, Liu TH, Ho CM, Liu CJ. Clinical practice guidelines and real-life practice for hepatocellular carcinoma in Taiwan. Clin Mol Hepatol. 2023 Apr;29(2):230-241

• April 27, 2024 (Sat) 14:10-14:25 •

The Association with iTACT-HBcrAg and HCC Risk after HBsAg Seroprevalence

Tetsuya Hosaka, Fumitaka Suzuki, Hiromitsu Kumada

Department of Hepatology, Toranomon Hospital, Tokyo, Japan

Hepatitis B core-related antigen (HBcrAg) is a unique biomarker which reflects the amounts of cccDNA and the transcriptional activity in the liver. A highly sensitive HB core-associated antigen assay (iTACT-HBcrAg) is now available in clinical practice in Japan. An ultra-sensitive assay for Hepatitis B surface antigen (iTACT-HBsAg) is also under development for clinical application. In this study, we aimed to elucidate the relationship between iTACT-HBcrAg measurement, iTACT-HBsAg, clinical course after HBsAg seroclearance measured by the conventional assay and the development of hepatocellular carcinoma (HCC). We enrolled 506 patients who were followed up for at least 3 months after achieving HBsAg seroclearance (conventional assay: ←0.05 IU/mL) and whose iTACT-HBcrAg was measured with stored serum (with or without antiviral therapy). The lower limit of quantification of iTACT-HBcrAg is 2.1 log U/mL, and that of iTACT-HBsAg is 0.0005 IU/mL. The median levels of iTACT-HBcrAg at HBsAg seroclearance were 2.6 in patients with antiviral therapy group and ←2.1 in those without antiviral therapy (P ← 0.001). On the other hand, there was no significant difference in iTACT-HBsAg levels between both groups. The incidence of HCC after HBsAg seroclearance was observed in 18 patients (3.9 thousand person-years). The cumulative HCC incidence rates wer significantly higher in patients with higher iTACT-HBcrAg than those with lower iTACT-HBcrAg (cut-off: 2,8 logU/mL, 7.0% vs 3.2% at 10 years, P = 0.024). The hazard ratio of patients with iTACT-HBcrAg →= 2.8 adjusted for age and cirrhosis was 3.45 (95%C.I.: 1.32-9.00) (Cox regression). On the other hand, the cumulative HCC incidence rate was marginally higher in patients with high iTACT-HBsAg and iTACT-HBcrAg ← 2.8 (P = 0.087). In concusion, iTACT-HBcrAg levels at HBsAg seroclearance by conventional assay were associated with subsequent HCC incidences.

Introducing the Presenter

Tetsuya Hosaka

Professor Hosaka has obtained M.D. degree in 1998 and started training as a physician of gastroenterology and Hepatology. After he obtained the certificate of gastroenterology and Hepatology in 2001, he enrolled Toranomon Hospital and started his research life about Hepatology. Currently, he is continuing research and also working as a clinical hepatologist in Toranomon Hospital. Their Institute is one of the largest liver centers and has the largest number of patients who are suffering from liver disease in Japan. He has been mainly working on the clinical research of hepatitis B and C, cirrhoisis and liver cancer. His professional memberships are American Association for the study of liver diseases (International member), Japan Society of Hepatology (councilor) and Japanese Society of Gastroenterology (councilor).

Research Interests

The main field of his research is related to HBV treatment, HBV markers and HBV-related liver cancer. Esspecially, he has been focusing on HCC risk reduction by antiviral therapy, the factors associated with HBV-related HCC development and functional cure of hepatitis B for a long time.

Publications

1. **Hosaka T**, Suzuki F, Kobayashi M, et al. Ultrasensitive Assay for Hepatitis B Core-Related Antigen Predicts Hepatocellular Carcinoma Incidences During Entecavir. Hepatol Commun 2022;6:36-49.
2. Tseng TC, **Hosaka T**, Liu CJ, et al. Hepatitis B Core-Related Antigen Stratifies the Risk of Liver Cancer in HBeAg-Negative Patients With Indeterminate Phase. Am J Gastroenterol 2022;117:748-757.
3. **Hosaka T**, Suzuki F, Kobayashi M, et al. Impact of hepatitis B core-related antigen on the incidence of hepatocellular carcinoma in patients treated with nucleos(t)ide analogues. Aliment Pharmacol Ther. 2019;49:457-471.
4. **Hosaka T**, Suzuki F, Kobayashi M, et al. Long-term entecavir treatment reduces hepatocellular carcinoma incidence in patients with hepatitis B virus infection. Hepatology. 2013;58:98-107.
5. **Hosaka T**, Suzuki F, Kobayashi M, et al. HBcrAg is a predictor of post-treatment recurrence of hepatocellular carcinoma during antiviral therapy. Liver Intl. 2010;30:1461-70.

• April 27, 2024 (Sat) 14:25-14:40 •

Enhancing Functional Cure: Retreating Off-Nuc Clinical Relapse with Pegylated Interferon

Wen-Juei Jeng

Department of Gastroenterology and Hepatology, Chang Gung Memorial Hospital, Linkou Medical Center, Taiwan; College of Medicine, Chang Gung University, Taiwan

Background and Aims:
HBsAg seroclearance significantly increases in HBeAg-negative chronic hepatitis B (CHB) patients who discontinue nucleos(t)ide analogue (NUC) therapy compared to rates observed during long-term viral suppression. The immune response following cessation of Nuc therapy may be influenced by the resurgence of viral antigens, thus aiding in the process of HBsAg reduction/seroclearance. It remained unknown whether treating off-Nuc clinical relapse (CR) patients with pegylated interferon, an immune-modulatory agent, would enhance the likelihood of achieving a functional cure. This study aims to investigate this issue comparing to those off-Nuc CR patients retreat with Nuc.
Method:
From the CGMH off-Nuc cohort, 25 HBeAg-negative CHB off-Nuc CR patients retreated with Peg-IFN (Rx-Peg-IFN) and 980 off-Nuc CR patients retreated with Nuc (Rx-Nuc) were enrolled. Propensity score matching (PSM) was employed, adjusting for age, gender, ALT, HBV DNA, and HBsAg levels at retreatment, between off-Nuc CR patients Rx-Peg-IFN and Rx-Nuc at a 1 to 3 ratio. Kaplan-Meier analysis and log-rank tests compared the cumulative HBsAg loss rate among these three groups.
Results:
After PSM, there were 25 and 75 patients in Rx-Peg-IFN and Rx-Nuc arms, respectively. The mean age was 50 of all both arms (P=0.63), 96% (Rx-Peg-IFN) and 86% (Rx-Nuc) were male (P=0.31). The median ALT level of Rx-Peg-IFN and Rx-NA were 156 and 162U/L (P=0.29), HBV DNA levels were 5.7 and 6.0 log10IU/mL (P=0.14), and HBsAg level was 2.8 and 3.3 log10IU/mL (P=0.62), respectively. The HBsAg reduction during the 1st year of retreatment was -1.14 versus -0.46 log10IU/mL, respectively, (P=0.0061). During a median follow-up of 7.1 years (from start of retreatment), 10 and 4 patients lost HBsAg in Rx-Peg-IFN and Rx-Nuc groups, respectively. The cumulative HBsAg seroclearance rates (from start of retreatment) at 1, 2, 5, and 10 years were 12%, 20.2%, 25.5%, and 45.0% in Rex-Peg-IFN arm, versus 0%, 0%, 2.7%, and 4.6% in Rex-Nuc arm, respectively (log rank test, P←.0001).
Conclusion:
Treating HBeAg-negative chronic hepatitis B (CHB) patients experiencing clinical relapse (CR) with Peg-IFN resulted in a notable increase in the rate of HBsAg loss (at the end of Peg-IFN treatment: 12%, and 1 year post-end of treatment: 20.2%). This highlights the potential of bolstering the off-Nuc immune response as a strategy to enhance functional cure.

Introducing the Presenter — Wen-Juei Jeng

Dr. Wen-Juei Jeng obtained her M.D. degree from National Yang-Ming University and received her PhD training from the same University. After completing her internal medicine residency and gastroenterology fellowship training at the Department of Gastroenterology and Hepatology in Chang Gung Memorial Hospital (CGMH), Linkou branch, Taiwan, she became an attending physician of Hepatology in 2010 and an Associate Professor in Chang Gung University. She currently serves as a Physician Scientist at CGMH since 2019.
Furthermore, she serves as the Deputy Director of Clinical Trial Center at CGMH. Dr. Jeng's research interests primarily lie in viral hepatitis, specifically HBV management, HBV finite treatment, new drugs clinical trials, and clinical/translational hepatology. She is an active member of TASL, EASL, and AASLD and has contributed to the peer-review process for numerous international journals.

Research Interests

Hepatitis B, Hepatocellular carcinoma

Publications

1. Liu YC, **Jeng WJ**, Peng CW, Chien RN, Liaw YF. Higher end-of-treatment HBsAg levels is associated with later onset but not severe relapse in HBeAg-negative chronic hepatitis B patients stopping antivirals. Aliment Pharmacol Ther. 2024 Jan 18. doi: 10.1111/apt.17880. Epub ahead of print. PMID: 38234285. **(Corresponding author)**
2. **Jeng WJ**, Chien RN, Chen YC et al. Hepatocellular carcinoma reduced, HBsAg loss increased and survival improved after finite therapy in hepatitis B patients with cirrhosis. Hepatology 2023 Aug 25. Doi: 10.1097/HEP.0000000000000575 epub.
3. **Jeng WJ**, Papatheodoridis GV, Lok ASF. Hepatitis B. Lancet 2023 Mar 25;401(10381):1039-1052.
4. **Jeng WJ**, Lok ASF. What will it take to cure hepatitis B? Hepatol Commun 2023 Mar 24; 7(4): e0084.
5. **Jeng WJ**, Chen YC, Chien RN, Sheen IS, Liaw YF. Incidence and predictors of HBsAg seroclearance after cessation of nucleos(t)ide analogue therapy in HBeAg negative chronic hepatitis B. Hepatology. 2018 Aug;68(2):425-434.

• April 27, 2024 (Sat) 14:40-14:55 •

HBsAg Decline Related to Immune Checkpoint Inhibitors in Cancer Patients

Hsien-Chen Mon[1], Pei-Chang Lee[1,2], Yi-Ping Hung[2,3,4], Ya-Wen Hung[5], Chi-Jung Wu[1,4], Chieh-Ju Lee6, Chen-Ta Chi[1,4], I-Cheng Lee[1,2], Ming-Chih Hou[1], Yi-Hsiang Huang[1,2,4,6*]

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[2] School of Medicine, College of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan
[3] Department of Oncology, Taipei Veterans General Hospital, Taipei, Taiwan
[4] Institute of Clinical Medicine, College of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan
[5] Health Examination Center, Taipei Veterans General Hospital, Taoyuan Branch, Taoyuan, Taiwan
[6] Healthcare and Services Center, Taipei Veterans General Hospital, Taipei, Taiwan

Background and aims: Immune checkpoint inhibitors (ICIs) can restore exhausted T cell immunity not only for cancer treatment but also potentially for curing chronic hepatitis B (CHB). Nowadays, ICIs are the mainstay of treatment for many cancer types, including HCC. It is currently unclear whether the immunomodulatory effects of ICIs can provide beneficial effect on HBV virological control or even HBsAg seroclearance, especially under oncological dosage of ICIs.

Methods: This study encompassed two cohorts for analysis, including Cohort 1: from May. 2016 to Aug. 2020, a retrospective consecutive 1350 cancer patients who received ICI treatment; and Cohort 2 (served as validation cohort): from Sep. 2020 to Oct. 2022, consecutive 162 prospectively enrolled HCC patients undergoing ICI treatment for a biomarker project. Patients should fulfill the following inclusion criteria: 1. HBsAg positive at the time of ICI treatment; 2. Available subsequent HBsAg data after ICIs; 3. At least one dose of ICIs for cancer treatment. Factors associated with HBsAg loss or combining HBsAg decline →1 log were analyzed.

Results: With median follow-up of 17.5 months, 8 (6.8%) in cohort 1 and 4 (9.1%) in cohort 2 achieved HBsAg seroclearance, and additional 4 in cohort 1 and 1 in cohort 2 had HBsAg decline →1 log. In multivariate analysis, HBsAg ←100 IU/mL was associated with HBsAg seroclearance (HR=6.274, p=0.028) or combining HBsAg decline →1 log. In the validation cohort, the cumulative incidence of HBsAg loss at months 12 and 24 was 13.0% and 38.4% for baseline HBsAg ←100 IU/ml. Of the 12 cases achieved HBsAg loss, the median cycles of ICIs were 16 (ranged 10 to 31), and the median time to HBsAg loss was 16.1 months (ranged 6.9 to 25.9). Importantly, none case with baseline HBsAg ↗100 IU/mL reached HBsAg loss within 24 months of ICIs treatment.

Conclusions: ICI is promising for HBsAg seroclearance, especially in patients with low HBsAg levels.

Introducing the Presenter — Yi-Hsiang Huang

Prof. Yi-Hsiang Huang is the President (2023-2027) of Taiwan Liver Cancer Association (TLCA), and the Director of Healthcare and Services Center at the Taipei Veterans General Hospital. He is also the Chair Professor for the Institute of Clinical Medicine, and the Director of the Department of Internal Medicine at the National Yang Ming Chiao Tung University. Completing his medical and PhD training at National Yang Ming University, he furthered his training as a research fellow at the Vaccine Branch of National Cancer Institute, National Institute of Health, USA from 2006 to 2007. Prof. Huang became a full professor at the Institute of Clinical Medicine, NYCU in 2011, and is now the Chair Professor at NYCU since Aug. 2022.
Prof. Huang has served as the council member of Asia-Pacific Primary Liver Cancer Expert Association (APPLE) since Jul. 2023; the executive committee member of Taiwan Association for the Study of the Liver (TASL) since Sep. 2023; the secretary general of the Chinese Medical Association (CMA) of Taiwan (2020-2026), the council member of the TLCA and the Taiwan Academy of Tumor Ablation (TATA). Prof. Huang has received numerous awards including academic awards of Prof. JL Sung's Research Foundation, physician research scholarships (Academic Sinica), merit scholarship awards (National Science Council), 2023 National Innovation Award, and 2024 National Healthcare Quality Award (Diamond Award) in recognition of his outstanding work. Prof. Huang was the Chief of Division of Gastroenterology and Hepatology, Taipei Veterans General Hospital from May 2017 to May 2023, the Chairman of 2019 TASL annual meeting, Chairman of 2020 TLCA annual meeting, Chairman of 2023 Gastroenterological Society of Taiwan (GEST) annual meeting

Research Interests

Prof. Huang's study interest is in the virology and immunology of viral hepatitis and HCC, including HBV reactivation related to immunosuppressive treatment and immune checkpoint inhibitors; and HCC treatment across locoregional to systemic therapy.

Publications

1. **Hung YW**, Lee IC, Chi CT, Lee RC, Liu CA, Chiu NC, Hwang HE, Chao Y, Hou MC, Huang YH*. Radiologic Patterns Determine the Outcomes of Initial and Subsequent Transarterial Chemoembolization in Intermediate-Stage Hepatocellular Carcinoma. Liver Cancer. 2024 Feb;13 (1): 29-40. (*corresponding author)
2. Lee PC, Wu CJ, **Hung YW**, Lee CJ, Chi CT, Lee IC, Yu-Lun K, Chou SH, Luo JC, Hou MC, Huang YH.*. Gut microbiota and metabolites associate with outcomes of immune checkpoint inhibitors-treated unresectable hepatocellular carcinoma. J Immunother Cancer 2022 Jun;10(6):e004779. (*corresponding author)
3. Chen MHan*, Lee IC, Chen MHuang, Hou MC, Tsai CY, **Huang YH***. Abatacept is second to rituximab at risk of HBsAg reverse seroconversion in patients with rheumatic disease. Annals of Rheumatic Diseases 2021 Nov;80(11):1393–1399. (*corresponding author)
4. Lee IC, Huang JY, Chen TC, Yen CH, Chiu NC, Hwang HE, Huang JG, Liu CA, Chau GY, Lee RC, Hung YP, Chao Y, Ho SY*, **Huang YH***. Evolutionary Learning Derived Clinical-Radiomic Models for Predicting Early Recurrence of Hepatocellular Carcinoma After Resection. Liver Cancer. 2021 Nov;10(6):572-582
5. Lee PC, Chao Y, Chen MH, Lan KH, Lee IC, Hou MC, **Huang YH***. Risk of HBV reactivation in patients with immune checkpoint inhibitor-treated unresectable hepatocellular carcinoma. J ImmunoTher Cancer 2020 Aug;8(2):e001072 (*corresponding author)

• April 27, 2024 (Sat) 14:55-15:10 •

Changes of Lipid Loading Capacity of Lipoproteins in Chronic Hepatitis B Patients Switching from TDF to TAF

Pin-Nan Cheng

Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan

Background: Switching from TDF to TAF leads to increase lipids in patients with chronic hepatitis B (CHB). The mechanisms underlying these features remain elusive.

Aim: This study aims to investigate the changes of lipid loading capacity of lipoproteins in patients switching from TDF to TAF or from entecavir (ETV) to TAF.

Methods: CHB patients on TDF or ETV who switched to TAF and no known dyslipidemia were prospectively enrolled. Demography and laboratory tests were recorded or performed at switch and at 48 weeks after switch to TAF. Their triglyceride (TG), cholesterol (Chol), and apoB levels were quantified in plasma samples and individually fractionated lipoprotein of various classes. the TG and Chol loading capacities were calculated with normalization to apoB, which represents per very low density lipoprotein (VLDL) and low density lipoprotein (LDL) particle unit.

Results: A total of 36 patients on TDF (n = 30) or ETV treatment (n = 6) were enrolled and followed up for 48 weeks after TAF switchover. Of the 36 patients, mean age was 55.4 years and 13 patients were females. At time of switch, TDF-experienced patients had lower serum levels of Chol and LDL than ETV-experienced patients. The switch from TDF to TAF significantly increased serum levels of TG, Chol, low density lipoprotein (HDL), and LDL, but the switch from ETV to TAF did not impact these parameters. In patients switching from TDF to TAF, the loading capacity of TG in VLDL significantly increased whereas the loading capacity of TG and Chol in LDL significantly declined. The difference of Chol loading capacity significantly decreased from 0.38 ± 1.53 of VLDL to -3.44 ± 3.50 of LDL ($p \leftarrow 0.001$). The difference of TG loading capacity also showed similar observation (1.17 ± 1.30 of VLDL vs. -0.75 ± 1.17 of LDL, $p \leftarrow 0.001$). The TG/Chol loading capacity in VLDL and LDL remained stationary in patients switching from ETV to TAF.

Conclusions: The changes of loading capacity of TG/Chol in VLDL and LDL may imply the association with increased lipids in CHB patients switching from TDF to TAF.

Introducing the Presenter — Pin-Nan Cheng

Prof. Pin-Nan Cheng graduated from Chung-Shan Medical University. He received full training of Internal Medicine and Hepatology in National Cheng Kung University Hospital. He is currently a full professor of College of Medicine, National Cheng University in Tainan of Taiwan since 2020 and is also the secretary general of Taiwan Association for the Study of the Liver (TASL) from 2023 to 2025. Prof. Cheng is a board member of Internal Medicine, Gastroenterology, TASL, the Taiwan Liver Cancer Association and the Taiwan Academy of Tumor Ablation.

Research Interests

Prof. Cheng's study interest is in the virology and clinical studies of viral hepatitis, MASLD, and hepatocellular carcinoma, including lipid profiles changes following HCV clearance, HBV reactivation following DAA treatment of HCV, real-world data of HCV treatment, outcomes of resected HCC in different etiology. He has published many original articles in international peer-review journals, including GUT, Clinical Gastroenterology and Hepatology, Alimentary and Pharmacology Therapeutics, Liver Cancer, Journal of Gastroenterology and Hepatology, and Journal of Microbiology, Immunology and Infection.

Publications

1. **Cheng PN**, Feng IC, Chen JJ, Kuo HT, Lee PL, Yu ML, Chiu YC, Chiu HC, Chien SC, Chen PJ, Liu CJ. (2024 Jan). Body weight increase and metabolic derangements after tenofovir disoproxil fumarate switch to tenofovir alafenamide in patients with chronic hepatitis B. Aliment Pharmacol Ther. 59(2):230-238.
2. **Cheng PN**, Chen WJ, Hou CJ, Lin CL, Chang ML, Wang CC, Chang WT, Wang CY, Lin CY, Hung CL, Peng CY, Yu ML, Chao TH, Huang JF, Huang YH, Chen CY, Chiang CE, Lin HC, Li YH, Lin TH, Kao CH, Wang TD, Liu PY, Wu YW, Liu CJ. (2024 Jan). Taiwan Association for the Study of the Liver-Taiwan Society of Cardiology Taiwan Position Statement for the Management of Metabolic Dysfunction-Associated Fatty Liver Disease and Cardiovascular Diseases. Clin Mol Hepatol. 30(1):16-36.
3. **Cheng PN**, Sun HY, Feng IC, Wang ST, Chiu YC, Chiu HC, Chien SC, Young KC. (2023 Feb). Reversibility of some oxidative stress markers in chronic hepatitis C patients after receiving direct-acting antiviral agents. J Virus Erad. 9(1):100318.
4. **Cheng PN**, Liu CJ, Chen CY, Tseng KC, Lo CC, Peng CY, Lin CL, Chiu HC, Chiu YC, Chen PJ. (2022 Dec). Entecavir Prevents HBV Reactivation During Direct Acting Antivirals for HCV/HBV Dual Infection: A Randomized Trial. Clin Gastroenterol Hepatol. 20(12):2800-2808.
5. Sun HY, **Cheng PN**, Tseng CY, Tsai WJ, Chiu YC, Young KC. (2018, Jul). Favouring modulation of circulating lipoproteins and lipid loading capacity by direct antiviral agents grazoprevir/elbasvir or ledipasvir/sofosbuvir treatment against chronic HCV infection. Gut. 67(7):1342-1350. (Co-first author)

• April 27, 2024 (Sat) 15:10-15:25 •

Recent Prevalence and Characteristics of Patients with Hepatitis Delta Virus in Japan

Naoya Sakamoto

Department of Gastroenterology and Hepatology, Hokkaido University, Japan

Although hepatitis delta virus (HDV) coinfection with hepatitis B virus (HBV) is a global health concern, the prevalence of HDV infections remains unknown due to insufficient data in many countries. In Japan, HDV prevalence has not been updated for over 20 years. We aimed to investigate the recent prevalence of HDV infections in Japan. Methods: We screened 1,264 consecutive patients with HBV infection at Hokkaido University Hospital between 2006 and 2022. Patients' serums were preserved and subsequently tested for IgG-HDV antibody. Available clinical information was collected and analyzed. We compared the changes in liver fibrosis using FIB-4 index between propensity-matched patients with and without the evidence of anti-HDV and corrected for baseline FIB-4 index, nucleoside/nucleotide analog treatment, alcohol intake, sex, HIV coinfection, liver cirrhosis, and age. Results: After excluding patients without properly stored serums and those lacking appropriate clinical information, 601 patients with HBV were included. Of these, 1.7% of patients had detectable anti-HDV. Patients with positive anti-HDV showed significantly higher prevalence of liver cirrhosis, lower prothrombin time, and higher prevalence of HIV coinfection than those who were negative for anti-HDV. A propensity-matched longitudinal analysis revealed that liver fibrosis (FIB-4 index) progressed more rapidly in patients with positive results for anti-HDV antibody tests. Conclusions: The recent prevalence of HDV infections in Japanese patients with HBV was 1.7% (10/601). These patients experienced rapid liver fibrosis progression, highlighting the importance of routine HDV testing.

Introducing the Presenter

Naoya Sakamoto

1987 Graduated from School of Medicine, Tokyo Medical and Dental University, Tokyo, Japan
1987-1993 Residency and fellowship at Second Department of Internal Medicine, Tokyo Medical and Dental University
1994-1996 Research fellowship at Division of Gastroenterology-Hepatology University of Connecticut Health Center, CT, USA
1996-2000 Clinical fellow at Second Department of Internal Medicine, Tokyo Medical and Dental University, Tokyo, Japan
2006 Associate professor at Department for Hepatitis Control, Tokyo Medical and Dental University
2012 Professor/Chairman at Department of Gastroenterology and Hepatology, Hokkaido University Graduate School of Medicine

Professional Societies

Director of the Japan Society of Hepatology
Director of the Japanese Society of Gastroenterology
Committee member of the Japanese Society of Internal Medicine
Committee member of the Liver Cancer Study Group of Japan
Director of the Japanese Association for Antiviral Therapy
Member of the American Association for the Study of Liver Diseases
Member of the American Society of Microbiology
Member of the Japanese Society of Gastroenterological Endoscopy

Journal Editor

Editorial director in chief of the Journal of Gastroenterology
Associate editor of the Hepatology Research
Associate editor of the Journal of Gastroenterology and Hepatology
Associate editor of Plos One
Editorial board member of the Antimicrobial Agents and Chemotherapy
Editorial board member of Hepatology International

Areas of Expertise

Molecular biology of hepatitis viruses
Clinical studies on viral hepatitis, NAFLD and HCCs

Special Lecture II

Masamichi Muramatsu (Japan)

Control of Hepatitis B Control: A Successful Example of Scientific, Medical, and Public Communities
Pei-Jer Chen (Taiwan)

• April 27, 2024 (Sat) 15:50-16:15 •

Introducing the Moderator

Masamichi Muramatsu

1993	Graduated from Akita University, Faculty of Medicine, and worked as a pediatrician
1995-1999	PhD student and Postdoc at Kyoto University (mentor; Professor Tasuku Honjo)
2002-2007	Assistant and Associate Professor at Kyoto University, Graduated School of Medicine
2007-2017	Professor at Kanazawa university, Graduate school of medical science, Japan
2017-2023	Director, Department of Virology II, NIID, Japan
2023.04.-	Professor, Department of Infectious Disease Research, Foundation for Biomedical Research and Innovation at Kobe

Research Interests

Molecular mechanism of virus-induced tumorigenesis, Viral DNA integration, Antiviral host defense against hepatitis viruses, Pathogenesis of hepatitis B virus infection

Publications

1. A versatile method to profile hepatitis B virus DNA integration. ***Hepatol. Commun*** 2023 Dec 1;7(12):e0328.
2. Interferon-gamma induced APOBEC3B contributes to Merkel cell polyomavirus genome mutagenesis in Merkel cell carcinoma. ***J Invest Dermatol*** 2022, Jul;142(7):1793-1803.e11.
3. Novel flavonoid hybrids as potent antiviral agents against hepatitis A: Design, synthesis and biological evaluation. ***Eur J Med Chem***. 2022 ;238:114452.
4. Flavonoid-triazolyl hybrids as potential anti-hepatitis C virus agents: Synthesis and biological evaluation. ***J. Med Chem*** 2021 5;218:113395.
5. NTCP oligomerization occurs downstream of the NTCP-EGFR interaction during hepatitis B virus internalization. ***J Virol***. 2021:JVI0093821.

• April 27, 2024 (Sat) 15:50-16:15 •

Control of Hepatitis B Control: A Successful Example of Scientific, Medical, and Public Communities

Pei-Jer Chen

Hepatitis Research Center, National Taiwan University and Hospital, Taiwan

Chronic hepatitis B was a prevalent, infectious liver disease in the world, especially high in the Asia-Pacific areas. With the advent of preventive vaccines and effective viral suppression drugs and active implementations, CHB has gradually become under control. The world-wide prevalence reduces from 4.2% in 1980 to 3.2% in 2020 study. CHB patients receiving long-term antiviral therapies significantly improve the clinical outcomes, saving from end-stage liver diseases. These progress has been possibly only through a close collaboration among scientific, medical and government officers. Despite of these impressive progresses, to meet the WHO sustained development goals (SDG) for CHB control, a 90% reduction of incidence and a 65% reduction of mortality in year 2030, there is still a long way to go. Four approaches are proposed: 1. A continuous monitoring of long-term vaccine efficacy in vaccinated populations; 2. Consolidating the HBV vaccination program against vaccine hesitancy and limited resources; 3. Rolling-out current oral antivirals to more CHB patients not only for diseases treatment but also for infection preventions; 4. Development of curative therapies, both friendly-to-dispense and affordable. A coherent and persevere effort by the three stakeholders achieve the SDG for CHB in the future.

Introducing the Presenter — Pei-Jer Chen

Professor Chen was appointed Director of the Hepatitis Research Center at the National Taiwan University Hospital in Taipei in 2001-2003, and now the faculty for Graduate Institute of Clinical Medicine, National Taiwan University. He was the President of Taiwan Association for Study of the Liver (TASL) from 2012 to 2013. He served as the President of Taiwan Society of Virology from 2016-2018.

Research Interests

His research interests cover on the molecular virology and immunology of hepatitis viruses, and the genetic and genomic study of hepatocellular carcinoma. Professor Chen's clinical research include the natural history of chronic viral hepatitis and hepatocellular carcinoma, and also explores and conducts new therapies and trials for both diseases. He has published over 680 articles in the areas of hepatitis and hepatocellular carcinoma.

Publications

1. Chung CY, Sun CP, Tao MH, Wu HL, Wang SH, Yeh SH, Zheng QB, Yuan Q, Xia NS, Ogawa K, Nakashima K, Tetsuro S, **Chen PJ**: A Major HBV Spliced RNA Encoding one Novel Protein Important for Infection. J of Hepatology. 2024 Feb 7:S0168-8278(24)00116-8.
2. Yeh SH, Li CL, Lin YY, Ho MC, Wang YC, Tseng ST, **Chen PJ**: Hepatitis B Virus DNA Integration Drives Carcinogenesis and Provides a New Biomarker for HBV-related HCC. Cell Mol Gastroenterol Hepatol. 2023;15(4):921-929.
3. Li CL, Hsu CL, Lin YY, Ho MC, Hu RH, Chen CL, Ho TC, Lin YF, Tsai SF, Tzeng ST, Huang CF, Wang YC, Yeh SH, **Chen PJ**: HBV DNA Integration into Telomerase or MLL4 Genes and TERT Promoter Point Mutation as Three Independent Signatures in Subgrouping HBV-Related HCC with Distinct Features. Liver Cancer. 2023 Apr 17;13(1):41-55.
4. Chen CY, Chuang WL, Qin A, Zhang WH, Zhu LY, Zhang GQ, Chen JJ, Lo CC, Zhou X, Mao X, Shang J, Kuo HT, Xie W, Chen CH, Lo GH, Jun DW, Dang S, Tsai CY, Wang TF, Lai HH, Tseng KC, Huang YW, **Chen PJ**: A Phase 3 clinical trial validating the potency and safety of an innovative, extra-long-acting interferon in chronic hepatitis C. JGH Open. 2022 Oct 10;6(11):782-791.
5. Wu CR, Kim HJ, Sun CP, Chung CY, Lin YY, Tao MH, Kim JH, Chen DS, **Chen PJ**: Mapping the conformational epitope of a therapeutic monoclonal antibody against HBsAg by in vivo selection of HBV escape variants. Hepatology. 2022 Jul;76(1):207-219.

Session 4

Molecular Virology

Chau-Ting Yeh (Taiwan), Koichi Watashi (Japan)

• April 27, 2024 (Sat) 16:15-17:45 •

Introducing the Moderator

Chau-Ting Yeh

Chau-Ting Yeh received his MD degree from National Taiwan University, Medical School in 1984. He earned his PhD degree from Department of Molecular Microbiology and Immunology, USC, UA, in 1992.
Afterward, he went back to Taiwan to serve in Chang Gung Memorial Hospital and became the attending doctor in Department of hepato-gastroenterology in 1993. He had been appointed as the Director of Hepatology Division in Department of hepato-gastroenterology, Director of digestive core lab in Liver Research Unit, and Director of Liver Research Center in this hospital. He is now holding the position of Acting Director, Institute of stem cell and translational cancer research in Chang Gung Memorial hospital.

Research Interests

- Hepatitis viruses
- Hepatocarcinogenesis
- Anticancer treatments in hepatocellular carcinoma

Publications

Correspondence

1. Lai MW, Chang YL, Cheng PJ, Chueh HY, Chang SC, **Yeh CT***. Absence of chronicity in infants born to immunized mothers with occult HBV infection in Taiwan. J Hepatol. 2022 Jul;77(1):63-70.
2. Lin CL, Chu YD, **Yeh CT***. Emergence of Oncogenic-Enhancing Hepatitis B Virus X Gene Mutants in Patients Receiving Suboptimal Entecavir Treatment. Hepatology. 2019 May;69(5):2292-2296.
3. Lai MW, Lin TY, Tsao KC, Huang CG, Hsiao MJ, Liang KH, **Yeh CT***. Increased seroprevalence of HBV DNA with mutations in the s gene among individuals greater than 18 years old after complete vaccination. Gastroenterology. 2012 Aug;143(2):400-7.
4. **Yeh CT***, So M, Ng J, Yang HW, Chang ML, Lai MW, Chen TC, Lin CY, Yeh TS, Lee WC. Hepatitis B virus-DNA level and basal core promoter A1762T/G1764A mutation in liver tissue independently predict postoperative survival in hepatocellular carcinoma. Hepatology. 2010 Dec;52(6):1922-33.
5. Hsu CW, **Yeh CT***, Chang ML, Liaw YF. Identification of a hepatitis B virus S gene mutant in lamivudine-treated patients experiencing HBsAg seroclearance. Gastroenterology. 2007 Feb;132(2):543-50.

• April 27, 2024 (Sat) 16:15-17:45 •

Introducing the Moderator

Koichi Watashi

2021.4-present	Director, Division of Drug Development, Research Center for Drug and Vaccine Development, National Institute of Infectious Diseases, Japan
2009.12-2021.3	Senior Researcher, Department of Virology II, National Institute of Infectious Diseases, Japan
2007.4-2009.11	Visiting Fellow, National Institutes of Health, USA (Mentor: Dr. Kuan-Teh Jeang)
2004.4-2007.3	Assistant Professor, Institute for Virus Research, Kyoto University
2003.11-2004.3	Instructor, Institute for Virus Research, Kyoto University
2003.4-2003.10	Post Doctoral Fellow, Japan Society of Promotion of Science (Mentor: Prof. Kunitada Shimotohno)
1998.4-2003.3	Kyoto University Graduate School of Pharmaceutical Science (Mentor: Prof. Kunitada Shimotohno)

Research Interests

- Molecular virology, Chemical biology, Antiviral drug development, Drug modalities
- Hepatitis B/C/D viruses, Coronaviruses, Flaviviruses, Poxviruses, Highly Pathogenic hemorrhagic fever viruses
- Virus entry, Virus-host interaction

Publications

1. Asami J, Park JH, Nomura Y, Kobayashi C, Mifune J, Ishimoto N, Uemura T, Liu K, Sato Y, Zhang Z, Muramatsu M, Wakita T, Drew D, Iwata S, Shimizu T, ***Watashi K**, *Park SY, *Nomura N, *Ohto U. Structural basis of hepatitis B virus receptor binding. Nat Struct Mol Biol 31(3): 447-454 (2024) (*corresponding author)
2. Park JH, Iwamoto M, Yun JH, Uchikubo-Kamo T, Son D, Jin Z, Yoshida H, Ohki M, Ishimoto N, Mizutani K, Oshima M, Muramatsu M, Wakita T, Shirouzu M, Liu K, Uemura T, Nomura N, Iwata S, **Watashi K**, Tame JRH, Nishizawa T, Lee W, Park SY. Structural insights into the bile acid transporter NTCP, the receptor for HBV. Nature 606(7916): 1027-1031 (2022)
3. Kobayashi C, Watanabe Y, Oshima M, Hirose T, Yamasaki M, Iwamoto M, Iwatsuki M, Asami Y, Kuramochi K, Wakae K, Aizaki H, Muramatsu M, Sureau C, Sunazuka T, ***Watashi K**. Fungal secondary metabolite exophillic acid selectively inhibits the entry of hepatitis B and D viruses. Viruses 14(4): 764 (2022) (*corresponding author)
4. Ji X, Jiang X, Kobayashi C, Ren Y, Hu L, Gao Z, Kang D, Jia R, Zhang X, Zhao S, ***Watashi K**, *Liu X, *Zhan P. Design, Synthesis, and Evaluation of a Set of Carboxylic Acid and Phosphate Prodrugs Derived from HBV Capsid Protein Allosteric Modulator NVR 3-778. Molecules 27(18): 5987 (2022) (*corresponding author)
5. Iwamoto M, Saso W, Nishioka K, Ohashi H, Sugiyama R, Ryo A, Ohki M, Yun JH, Park SY, Ohshima T, Suzuki R, Aizaki H, Muramatsu M, Matano T, Iwami S, Sureau C, Wakita T, ***Watashi K**. The machinery for endocytosis of epidermal growth factor receptor coordinates the transport of incoming hepatitis B virus to the endosomal network. J Biol Chem 295(3): 800-807 (2020) (*corresponding author)

• April 27, 2024 (Sat) 16:15-16:30 •

Tripartite Motif-Containing Protein 21 Regulates Hepatocyte Nuclear Factors, Thereby Contributes to IFN-γ-Induced Suppression of HBV

Juhee Won[1, 2], Hong Seok Kang[2], Na Yeon Kim[1], Mehrangiz Dezhbord[1], MK Gayashan[1], Soree Park[1], Dong-Sik Kim, Kyun-Hwan Kim

[1]Department of Precision Medicine, School of Medicine, Sungkyunkwan University, Suwon, Republic of Korea
[2]Department of Pharmacology, Center for Cancer Research and Diagnostic Medicine, IBST, School of Medicine, Konkuk University, Seoul, Republic of Korea
[3]Division of HBP Surgery and Liver Transplantation, Department of Surgery, Korea University College of Medicine, Seoul, Republic of Korea

The antiviral role of the tripartite motif (TRIM) family protein, a member of the E3-ubiquitin ligase family, has recently been actively studied. Hepatitis B virus (HBV) infection is a major contributor to liver diseases; however, the host factors regulated by cytokine-inducible TRIM21 to suppress HBV remain unclear. In this study, we showedthe antiviral efficacy of TRIM21 against HBV in hepatoma cell lines, primary human hepatocytes (PHHs) isolated from patient liver tissues, and mouse model. Using TRIM21knock-out cells, we confirmed that the antiviral effects of IFN-γ, which suppress HBV replication, are abolishedwhen TRIM21 is deficient. Northern blot analysis confirmed a reduction of HBV RNA levels by TRIM21. Using Luciferase reporter assay, we also discovered that TRIM21 decreases the activity of HBV enhancers, which play a crucial role in cccDNA transcription. The participation of the RING domain and PRY-SPRY domain in the anti-HBV effect of TRIM21 was demonstrated through experiments using deletion mutants. We identified a novel interaction between TRIM21 and HNF4αthrough co-immunoprecipitation assay. More specifically, ubiquitination assay revealed that TRIM21 promotes ubiquitin-mediated proteasomal degradationof HNF4α. HNF1α transcription is downregulated as a result of the degradation of HNF4α, an activator for the HNF1α promoter. Therefore,the reduction of key HBV enhancer activators, HNF4α and HNF1α, by TRIM21 resulted in a decline in HBV transcription, ultimately leading to the inhibition of HBV replication.

Introducing the Presenter — Juhee Won

Department of Pharmacology, School of Medicine,
Konkuk University Graduate School joint MS and Ph.D course

Research Interests

- Hepatitis B virus
- Drug resistance
- Hepatocellular carcinoma

Publication

1. Won J, Lee AR, Dezhbord M, Lee DR, Kim KH et al, Susceptibility of drug resistant hepatitis B virus mutants to besifovir, Biomedicines , 2022
2. Kim JC, Lee AR, Dezhbord M, Won J, Park S, Kim NY, Kim KH et al, Identification and characterization of besifovir-resistant hepatitis B virus lsolated from a chronic hepatitis B patient, Biomedicines, 2022
3. Lee AR, Cho JY, Won J, Kim DS, Lee JH, Kim KH et al, Distinctive HBV replication capacity and susceptibility to tenofovir induced by a polymerase point Mutation in hepatoma cell lines and primary human hepatocytes, Int J Mol Sci, 2021
4. Park S, Ha YN, Won J, Kim KH et al, Suppression of Hepatocyte nuclear factor 4α by long-term infection of hepatitis B virus contributes to tumor cell proliferation, Int J Mol Sci, 2020
5. Park ES, Lee AR, Kim DH, Park S, Won J, Ha YN, Kim KH et al, Identification of a quadruple mutation that confers tenofovir resistance in chronic hepatitis B patients, J Hepatol, 2019

• April 27, 2024 (Sat) 16:30-16:45 •

Why Macaque-Derived NTCP Cannot Function as an HBV Receptor?

Kaho Shionoya[1,2,3], Jae-Hyun Park[4], Toru Ekimoto[5], Junko S. Takeuchi[6], Junki Mifune[3], Takeshi Morita3, Naito Ishimoto[4], Haruka Umezawa[4], Kenichiro Yamamoto[5], Chisa Kobayashi[1,2,3], Atsuto Kusunoki[3], Norimichi Nomura[7], So Iwata[7], Masamichi Muramatsu[1,8], Jeremy R.H. Tame[4], Mitsunori Ikeguchi[5], Sam-Yong Park4, Koichi Watashi[1,2,3]

[1]Department of Virology II, National Institute of Infectious Diseases, Japan.
[2]Graduate School of Science and Technology, Tokyo University of Science, Japan.
[3]Research Center for Drug and Vaccine Development, National Institute of Infectious Diseases, Japan.
[4]Drug Design Laboratory, Graduate School of Medical Life Science, Yokohama City University, Japan.
[5]Computational Life Science Laboratory, Graduate School of Medical Life Science, Yokohama City University, Japan.
[6]Center for Clinical Sciences, National Center for Global Health and Medicine, Japan.
[7]Department of Cell Biology, Graduate School of Medicine, Kyoto University, Japan.
[8]Department of Infectious Disease Research, Foundation for Biomedical Research and Innovation at Kobe, Japan

Hepatitis B virus (HBV) infects hepatocytes of limited animals such as human and chimpanzee, but not most old-world monkey species including cynomolgus macaque (crab-eating monkey). HBV is restricted in cynomolgus macaque at virus-cell attachment step because HBV preS1 cannot bind to macaque-derived NTCP (mNTCP). However, in spite of having 96% identity to human-derived NTCP (hNTCP), how mNTCP obstructs viral binding is unknown. In this study, we solved the cryo-electron microscopy (cryo-EM) structure of the mNTCP–bile acid complex. Superposing this complex on that of the hNTCP–preS1 complex, which was recently revealed (Asami et al. Nat Struct Mol Biol 2024), showed that Arg158 of mNTCP induced steric clash with the preS1 main-chain. Cell-based infection assays confirmed that only glycine at position 158 allowed preS1 to embed deeply into the hydrophobic tunnel of NTCP, but this site was distal to the bile acid-binding pocket and could vary for the transporter function. Additionally, molecular dynamics simulation using our cryo-EM structures of NTCP-preS1 complex showed Lys86 in hNTCP on the extracellular region dynamically stabilized the binding state of preS1. Moreover, NTCP-bound bile acids induced steric clash with preS1 through their tailed-chain, explaining the strong anti-HBV activity of long-chain conjugated-bile acids. This study presents structural insights in which two different sites are coordinately involved in NTCP-preS1 binding, and mNTCP loses the preS1 binding activity at both sites. These information are useful for understanding the strict host specificity of HBV and for developing the anti-HBV strategy by targeting viral entry.

Introducing the Presenter — Kaho Shionoya

2016-2020	Tokyo University of Science, Faculty of Science and Technology
2019-2023	National Institute of Infectious Diseases, Department of Virology II
2020-present	Tokyo University of Science, Graduate School of Science and Technology
2022-present	Research Fellowship for Young Scientists, Japan Society for the Promotion of Science
2023-present	National Institute of Infectious Diseases, Research Center for Drug and Vaccine Development

Research Interests

Hepatitis B virus, Virus entry, Virus-host interaction, Species specificity

Publications

1. Akazawa D, Ohashi H, Hishiki T, Morita T, Iwanami S, Kim KS, Jeong YD, Park ES, Kataoka M, **Shionoya K**, Mifune J, Tsuchimoto K, Ojima S, Azam AH, Nakajima S, Park H, Yoshikawa T, Shimojima M, Kiga K, Iwami S, Maeda K, Suzuki T, Ebihara H, Takahashi Y, Watashi K: Potential Anti-Mpox Virus Activity of Atovaquone, Mefloquine, and Molnupiravir, and Their Potential Use as Treatments. J Infect Dis. 228(5): 591-603 (2023).
2. Ohashi H, Hishiki T, Akazawa D, Kim KS, Woo J, **Shionoya K**, Tsuchimoto K, Iwanami S, Moriyama S, Kinoshita H, Yamada S, Kuroda Y, Yamamoto T, Kishida N, Watanabe S, Hasegawa H, Ebihara H, Suzuki T, Maeda K, Fukushi S, Takahashi Y, Iwami S, Watashi K: Different efficacies of neutralizing antibodies and antiviral drugs on SARS-CoV-2 Omicron subvariants, BA.1 and BA.2. Antiviral Res. 205: 105372 (2022).
3. **Shionoya K**, Yamasaki M, Iwanami S, Ito Y, Fukushi S, Ohashi H, Saso W, Tanaka T, Aoki S, Kuramochi K, Iwami S, Takahashi Y, Suzuki T, Muramatsu M, Takeda M, Wakita T, Watashi K: Mefloquine, a Potent anti-Severe Acute Respiratory Syndrome-related Coronavirus 2 (SARS-CoV-2) drug as an entry inhibitor in vitro. Front Microbiol. 12: 651403 (2021).
4. Iwanami S, Kitagawa K, Ohashi H, Asai Y, **Shionoya K**, Saso W, Nishioka K, Inaba H, Nakaoka S, Wakita T, Diekmann O, Iwami S, Watashi K: Should a viral genome stay in the host cell or leave? A quantitative dynamics study of how hepatitis C virus deals with this dilemma. PLoS Biol. 18(7): e3000562 (2020).

• April 27, 2024 (Sat) 16:45-17:00 •

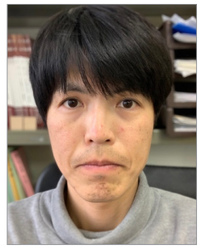
TRIM26 Supports HBV Replication by Preventing Core Protein from Proteasome-Dependent Degradation

Yuki Nakaya

Division of Virology, Department of Infection and Immunity, Faculty of Medicine, Jichi Medical University, Japan

Chronic hepatitis B virus (HBV) infection is a major medical concern worldwide. Current treatments for HBV infection effectively inhibit virus replication; however, these treatments cannot eradicate covalently closed circular DNA and novel treatment-strategies need to be developed. Here we identified tripartite motif-containing protein 26 (TRIM26) could be a supportive factor for HBV replication. Small interfering RNA-mediated TRIM26 knockdown (KD) modestly impaired HBV replication in hepatocytes. Endogenous TRIM26 physically interacted with HBV core protein (HBc), but not polymerase and HBx, via the SPRY domain of TRIM26. Surprisingly, TRIM26 inhibited HBc ubiquitination even though TRIM26 is an E3 ligase. HBc was degraded by TRIM26 KD in Huh-7 cells, whereas the reduction was restored by a proteasome inhibitor. RING domain-deleted TRIM26 mutant (TRIM26ΔR), a dominant negative form of TRIM26, promoted HBc degradation by sequestering TIRM26 from HBc. In summary, we demonstrated that HBV TRIM26 to excape from the proteasome-dependent HBc degradation. The interaction between TRIM26 and HBc might be a new therapeutic target against HBV infection.

Introducing the Presenter — Yuki Nakaya



Current Position

Division of Virology, Department of Infec6on and Immunity, Faculty of Medicine, Jichi Medical University, Japan

Education

2002-2008 Bachelor of Veterinary Medicine, Iwate University, Morioka, Japan
2008 Doctor of Veterinary Medicine, Ministry of Agriculture, Forestry and Fisheries, Tokyo, Japan
2008-2011 Ph.D. in Medicine, Kyoto University, Kyoto, Japan

Experience

2011-2014 Postdoc, Institute for Virus Research, Kyoto University, Kyoto, Japan
2014-2016 Postdoc, Perelman school of Medicine, University of Pennsylvania, Philadelphia, USA
2016-2017 Postdoctoral Research Associate, Department of Microbiology and Immunology, University of Illinois at Chicago, Chicago, USA
2017-2021 Senior scien6st, National Institute of Advanced Industrial Science and Technology, Tsukuba, Japan
2021- Assistant professor, Division of Virology, Department of Infection and Immunity, Faculty of Medicine, Jichi Medical University, Shimotsuke, Japan

Research Interests

- Hepa66s B virus
- Endogenous virus
- Host-virus interac6on

Publications

1. 2011-2014 Postdoc, Institute for Virus Research, Kyoto University, Kyoto, Japan
2. 2014-2016 Postdoc, Perelman school of Medicine, University of Pennsylvania, Philadelphia, USA
3. 2016-2017 Postdoctoral Research Associate, Department of Microbiology and Immunology, University of Illinois at Chicago, Chicago, USA
4. 2017-2021 Senior scien6st, National Institute of Advanced Industrial Science and Technology, Tsukuba, Japan
5. 2021- Assistant professor, Division of Virology, Department of Infection and Immunity, Faculty of Medicine, Jichi Medical University, Shimotsuke, Japan

• April 27, 2024 (Sat) 17:00-17:15 •

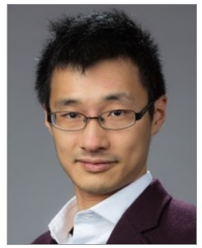
Epitranscriptomic Cytidine Methylation of the Hepatitis B Viral RNA Packaging Signal Is Essential for Viral Reverse Transcription

Pei-Yi (Alma) Su[1], Shin-Chwen Bruce Yen[1], Chih-Hsu Chang[1], Wan-Ju Tung[1], Hsiu-Yi Wu[1], Yu-Pei Hu[1], Yen-Yu Ian Chen[1], Miao-Hsia Lin[2], Chiaho Shih[3], Pei-Jer Chen[4], Kevin Tsai[1]

[1]Institute of Biomedical Sciences (IBMS), Academia Sinica, Taiwan,
[2]Graduate Institute and Department of Microbiology, National Taiwan University College of Medicine, Taiwan,
[3]Graduate Institute of Cell Biology, College of Life Sciences, China Medical University, Taiwan,
[4]Hepatitis Research Center, National Taiwan University College of Medicine, Taiwan

Epitranscriptomic RNA modifications have emerged as important regulators of the fate and function of viral RNAs. One prominent modification, the cytidine methylation 5-methylcytidine (m^5C), is found on the RNA of HIV-1, where m^5C enhances the translation of HIV-1 RNA. However, whether m^5C functionally enhances the RNA of other pathogenic viruses remains elusive. Here, we report that the RNA of hepatitis B virus (HBV) is enriched with m^5C at stoichiometries much higher than host mRNA, mainly deposited by the cellular methyltransferase NSUN2. Intriguingly, m^5C is mostly found on the epsilon hairpin, an RNA element required for viral RNA encapsidation and reverse transcription. Loss of m^5C from HBV RNA due to NSUN2 depletion, resulted in a modest decrease in viral core protein (HBc) production, yet this is accompanied by a near-complete loss of the reverse transcribed viral DNA. Similarly, mutations introduced to remove the methylated cytidines resulted in a translation decrease and block of reverse transcription. Furthermore, pharmacological disruption of m^5C deposition led to a significant decrease in HBV replication. Thus, our data indicates m^5C methylations is a critical mediator of the epsilon element in HBV reverse transcription, suggesting the therapeutic potential of targeting the m^5C methyltransfer process on the HBV 5'epsilon as an antiviral strategy.

Introducing the Presenter — Kevin Tsai



2008–2014	Ph.D., Cell and Molecular Biology Graduate Group, University of Pennsylvania *Tegument protein BNRF1 regulation of Epstein-Barr virus genome chromatinization during early infection* Advisor: Paul M. Lieberman, Ph.D.
2014–2021	Postdoctoral Scholar, Duke University Medical Center Epitranscriptomic RNA modifications in HIV-1 & SV40 infections Advisor: Bryan R. Cullen, Ph.D.
2021–current	Assistant Research Fellow, Institute of Biomedical Sciences, Academia Sinica

Research Interests

Epitranscriptomic RNA modifications, RNA metabolism, virus-host interactions, Influenza A virus, Hepatitis B virus, HIV-1, Retrovirology

Publications

1. Epitranscriptomic addition of m6A regulates HIV-1 RNA stability and alternative splicing. **Tsai K**, Bogerd HP, Kennedy EM, Emery A, Swanstrom R, Cullen BR. **Genes Dev**. 2021
2. Acetylation of cytidine residues boosts HIV-1 gene expression by increasing viral RNA stability. **Tsai K**, Vasudevan AJ, Martinez Campos C, Emery A, Swanstrom R, Cullen BR. **Cell Host Microbe**. 2020
3. Epitranscriptomic addition of m^5C to HIV-1 transcripts regulates viral gene expression. Courtney DG, **Tsai K**, Bogerd HP, Kennedy EM, Law BA, Emery A, Swanstrom R, Holley CL, Cullen BR. **Cell Host Microbe**. 2019
4. Influenza A virus-derived siRNAs increase in the absence of NS1 yet fail to inhibit virus replication. **Tsai K**, Courtney DG, Kennedy EM, Cullen BR. **RNA**. 2018
5. Addition of m6A to SV40 late mRNAs enhances viral structural gene expression and replication. **Tsai K**, Courtney DG, Cullen BR. **PLoS Pathog**. 2018

• April 27, 2024 (Sat) 17:15-17:30 •

Alteration of Gene Expression after Entecavir and Pegylated Interferon Therapy in HBV-Infected Chimeric Mouse Liver

Masataka Tsuge

Department of Gastroenterology, Graduate School of Biomedical and Health Sciences, Hiroshima Univ., Hiroshima, Japan

Background and aims: Cross-sectional nature analyses using liver tissue from chronic hepatitis B patients make it difficult to exclude the influence of host immune responses. In this study, we analyzed the alteration of gene expression in the livers of hepatitis B virus (HBV)-infected uPA/SCID mice with humanized livers before and after antiviral therapy with entecavir and pegylated interferon.

Methods: Eleven chimeric mice with human hepatocytes were prepared, and 6 of the mice were inoculated with 106 genome copies of HBV genotype C. The remaining 5 uninfected mice were sacrificed to assess baseline gene expression. Three HBV-infected mice were sacrificed after HBV DNA had plateaued. The remaining 3 HBV-infected mice were sacrificed after HBV DNA had fallen to undetectable levels following antiviral therapy. Human hepatocytes were dissected from the mouse livers, and gene expression was assessed by next-generation sequencing (NGS).

Results: After HBV infection, expression of genes involved in the gonadotropin-releasing hormone receptor pathway, CCKR signaling, integrin signaling, the inflammation pathway, and T cell activation were significantly altered in HBV-infected livers. After antiviral therapy, levels of 37 out of 89 genes downregulated by HBV infection were restored, and 54 of 157 genes upregulated by HBV infection were suppressed. Interestingly, genes associated with hypoxia and KRAS signaling were included among the 54 genes upregulated by HBV infection and downregulated by antiviral therapy.

Conclusion: Several genes associated with cell growth or carcinogenesis via hypoxia and KRAS signaling were significantly downregulated by antiviral therapy, with potential application to suppression of hepato-carcinogenesis.

Introducing the Presenter — Masataka Tsuge

EDUCATIONS

1992-1998 Hiroshima University (Faculty of Medicine)
2002-2006 Graduate School of Hiroshima University (Division of Frontier Medical Science)

SCIENTIFIC TRAINING

2005-2006 The Institute of Medical Science, The University of Tokyo (Research student)
2018 Loyola University Medical Center (collaborator)

POSITIONS

2006-2007 Research resident, Viral Hepatitis Research Foundation, Japan
2007-2008 Assistant Professor, Dept. of Gastroenterology and Metabolism, Hiroshima University Hospital
2009-2021 Assistant Professor, Natural Science Center for Basic Research and Development, Hiroshima University, Japan
2021-2023 Lecture, Department of Biomedical Science, Research and Development Division, Natural Science Center for Basic Research and Development, Hiroshima University
2023 - Associate Professor, Department of Gastroenterology, Graduate School of Biomedical & Health Sciences, Hiroshima University

Research Interests

- Hepatitis B Virus
- Hepatitis C Virus
- Liver disease

• April 27, 2024 (Sat) 17:30-17:45 •

Examination of Lipid Nanoparticles Loading Ribonucleoprotein-Oligonucleotide Complexes for Genome Editing to Hepatitis B Virus Inhibition *in vitro* and *in vivo*

Tsukiyama-Kohara K.[1*], Kayesh MEH.[1, 2], Sato Y.[2], Harashima H.[3], Kohara M.[4]

[1]Kagoshima University, [2]Patuakhali University, [3]Hokkaido University, [4]Tokyo Metropolitan Institute of Medical Science, Japan

Clustered regularly interspaced short palindromic repeats (CRISPR)-associated (Cas) system has considerable therapeutic potential in a wide range of intractable genetic diseases and infectious diseases including hepatitis B virus (HBV) infection. While non-viral delivery technologies for the CRISPR/Cas system are expected for its clinical translation, difficulty of clinically relevant synthesis of formulations and poor efficiency of delivery severely hinder therapeutic genome editing. Here, we characterized a lipid nanoparticle (LNP)-based CRISPR/Cas ribonucleoprotein (RNP) delivery nanoplatform synthesized by a clinically relevant process using a mixer-equipped microfluidic device. Loss of DNA cleavage activity and aggregation of Cas enzyme was fully avoided under the optimized synthetic condition. The optimized formulation, which was identified through 2 steps of design of experiments, exhibited excellent gene disruption (up to 97%) and base substitution without any apparent cytotoxicity. Addition of negative charges to RNPs by complexing single-stranded oligonucleotide (ssON) significantly enhanced delivery of both Cas9 and Cpf1 RNPs. Furthermore, the optimized formulation significantly suppressed both HBV DNA and covalently closed circular DNA (cccDNA) in HBV-infected human liver cells. These findings will greatly contribute to the development of RNP as an efficient delivery tool for CRISPR/Cas delivery and its practical application in the CRISPR/Cas-based gene therapy. We are now optimizing RNP for *in vivo* delivery.

Introducing the Presenter

Kyoko Tsukiyama-Kohara

Doctoral degree(s)

Ph.D. 09/2014 Kumamoto University, Kumamoto, Japan
Ph.D. 06/1989 The University of Tokyo, Tokyo, Japan
D.V.M. 06/1985 National Veterinary License, Japan

Other degree(s)

B.Sc 03/1983 Hokkaido University, Sapporo, Japan
M.Sc 03/1985 Hokkaido University, Sapporo, Japan

10/2011	Present	Kagoshima University Professor, Director, TAD Center
10/2005	9/2011	Kumamoto University Professor, Virology, Molecular biology,
09/2000	09/2005	Institute of Medical Science, The University of Tokyo, Lecturer, Virology, Molecular biology
10/1994	12/1996	Department of Biochemistry (Professor Nahum Sonenberg), McGill University, Postdoctoral fellow, Molecular biology
04/1990	08/2000	The Tokyo Metropolitan Institute of Medical Science, Researcher, Virology, Molecular biology
04/1988	03/1990	TONEN General Research Institute Co. Researcher, Virology, Molecular biology

Expertise Key Words: Virus, HCV, HCC, HBV, DENV, Vaccine, Animal model, Tupaia

Publications

***Corresponding author**

1. Uno Y, Jikuya S, Noda Y, Oguchi A, Murayama N, Kawaguchi H, **Tsukiyama-Kohara K**, Yamazaki H. Newly identified cytochrome P450 3A genes of tree shrews and pigs are expressed and encode functional enzymes. Comp Biochem Physiol C Toxicol Pharmacol. 2023 Feb 22;267:109579. doi: 10.1016/j.cbpc.2023.109579.
2. Uno Y, Noda Y, Murayama N, **Tsukiyama-Kohara K**, Yamazaki H. Novel cytochrome P450 1 (CYP1) genes in tree shrews are expressed and encode functional drug-metabolizing enzymes. Comp Biochem Physiol C Toxicol Pharmacol. 2023 Mar;265:109534. doi: 10.1016/j.cbpc.2022.109534.
3. Kitab B, **Tsukiyama-Kohara K***. Regulatory Role of Ribonucleotide Reductase Subunit M2 in Hepatocyte Growth and Pathogenesis of Hepatitis C Virus. Int J Mol Sci. 2023 Jan 30;24(3):2619. doi: 10.3390/ijms24032619.PMID: 36768940
4. Ushirozako G, Noda Y, Murayama N, Kawaguchi H, **Tsukiyama-Kohara K**, Yamazaki H, Uno Y. Newly Identified Tree Shrew Cytochrome P450 2A13 (CYP2A13) is Expressed in Liver and Lung and Encodes a Functional Drug-Metabolizing Enzyme Similar to Dog CYP2A13 and Pig CYP2A19. Drug Metab Dispos. 2023 Jan 20:DMD-AR-2022-001152. doi: 10.1124/dmd.122.001152.
5. Kayesh MEH, Khalil I, Kohara M, **Tsukiyama-Kohara K***. Increasing Dengue Burden and Severe Dengue Risk in Bangladesh: An Overview. Trop Med Infect Dis. 2023 Jan 3;8(1):32. doi: 10.3390/tropicalmed8010032.

Day 2. Sunday, April 28, 2024
Woo Duck Yoon Duck Byung Hall, Biomedical Research Institute, Seoul National Univ. Hospital

Session 5

Immunology

Masanori Isogawa (Japan), Eui-Cheol Shin (Korea)

HBV-Specific Tissue-Resident Memory T Cells in Human HBV-Infected Liver Diseases
Yang Cheng (Taiwan)

Liver Sinusoidal T Cells in Healthy and HBV-Infected Livers
Eui-Cheol Shin (Korea)

Selection of Viral Escape Mutants by $CD8^+$ T Cells in HBeAg-Negative Chronic Hepatitis B Patients
Hung-Chih Yang (Taiwan)

Direct Analysis of Human Hepatic Stellate Cells by Flow Cytometry
Hideki Ueno (Japan)

Distinct NK-like Liver Sinusoidal $CD56^{hi}CD8^+CD161^-$ T Cells Expanded in Patient with HBV Infection
June-Young Koh (Korea)

Strategic Direction: Alliance to Combating Vertical Transmission of Hepatitis B in Tanzania – Mobilizing Support from Asia to Africa
Jin Yong Kim (Korea)

• April 28, 2024 (Sun) 09:00-10:30 •

Introducing the Moderator

Masanori Isogawa

Dr. Masanori Isogawa, M.D., Ph.D., graduated from Mie University School of Medicine in 1998. Following a brief residency in Internal Medicine, he started his research career at the Institute for Virology in Essen University Hospital in 1999. In 2001, he relocated to La Jolla, CA, USA, to join the Chisari Laboratory at the Scripps Research Institute (TSRI), renowned for its groundbreaking work in hepatitis research. Utilizing various mouse models of hepatitis B virus (HBV) infection, Dr. Isogawa made seminal contributions to elucidating the impact of intrahepatic antigen recognition on HBV-specific CD8 T cells. These achievements led to his appointment as Assistant Professor at TSRI. With Dr. Chisari, Dr. Isogawa then generated HBV-specific T cell receptor transgenic mice, uncovering that HBV-specific T cell priming in the liver induces T cell tolerance. This model, established by him and adopted by other research groups, significantly advanced our understanding of liver-mediated T cell tolerance. In 2013, Dr. Isogawa returned to Japan to join Dr. Tanaka's group at Nagoya City University, one of Japan's leading laboratories in HBV research. In 2020, he moved to the Department of Immunology at the National Institute of Infectious Diseases, focusing on dissecting immune responses to COVID-19 infections and vaccinations. In 2024, Dr. Isogawa was appointed to his current position, where he directs basic research on hepatitis and diarrhea viruses. His primary interests lie in unraveling the molecular and cellular mechanisms of chronic virus infections and in the development of therapeutic vaccines against chronic HBV infection.

Research Interests

T cell, tolerance, Antigen recognition, Therapeutic vaccination

Publications

1. Kotaki R, **Isogawa M**, Takahashi Y, et al. SARS-CoV-2 Omicron-neutralizing memory B cells are elicited by two doses of BNT162b2 mRNA vaccine. Sci Immunol. 2022 Apr 22;7(70):eabn8590.
2. Baudi I, **Isogawa M**, Tanaka Y, et al., Interferon signaling suppresses the unfolded protein response and induces cell death in hepatocytes accumulating hepatitis B surface antigen. PLoS Pathog. 2021 May 12;17(5):e1009228.
3. Kawashima K, **Isogawa M**, Tanaka Y, et al. Restoration of type I interferon signaling in intrahepatically primed CD8+ T cells promotes functional differentiation. JCI Insight. 2021 Feb 8;6(3):e145761.
4. **Isogawa M**, Chung J, Murata Y, Kakimi K, Chisari FV. CD40 activation rescues antiviral CD8+ T cells from PD-1-mediated exhaustion. PLoS Pathog. 2013;9(7):e1003490. doi: 10.1371/journal.ppat.1003490.
5. **Isogawa M**, Furuichi Y, Chisari FV. Oscillating CD8(+) T cell effector functions after antigen recognition in the liver.
   Immunity. 2005 Jul;23(1):53-63. doi: 10.1016/j.immuni.2005.05.005. PubMed PMID: 16039579

• April 28, 2024 (Sun) 09:00-10:30 •

Introducing the Moderator

Eui-Cheol Shin

Prof. Eui-Cheol Shin received his M.D. (1996) and Ph.D. (2001) from Yonsei University College of Medicine, Seoul, Republic of Korea, and his postdoctoral training from NIDDK, National Institutes of Health, Bethesda, Maryland, USA. Then he joined Graduate School of Medical Science and Engineering, Korea Advanced Institute of Science and Technology (KAIST), Daejeon, Republic of Korea in 2007, where he is currently a professor. He is also the director of the Center for Viral Immunology, Korea Virus Research Institute, Institute for Basic Science (IBS), Daejeon, Republic of Korea, since 2021. Prof. Shin was elected as a member of The Korea Academy of Science and Technology and The National Academy of Medicine of Korea in 2019 and 2024, respectively.

Research Interests

T cell-mediated immunopathogenesis, senescence of T cells, reinvigoration of exhausted T cells, and immune responses in viral hepatitis and COVID-19

Publications

1. Kim SH, Kim J, Jung S, Noh JY, Kim J, Park H, Song YG, Peck KR, Park SH, Park MS, Ko JH, Song JY, Choi JY, Jung MK, **Shin EC**. Omicron BA.2 breakthrough infection elicits CD8+ T cell responses recognizing the spike of later Omicron subvariants. Sci Immunol 9:eade6132, 2024
2. Lee H, Jung MK, Noh JY, Park SH, Chung Y, Ha SJ, **Shin EC**. Better understanding CD8+ T cells in cancer and viral infections. Nat Immunol 24:1794-1796, 2023
3. Koh JY, Rha MS, Choi SJ, Lee HS, Han JW, Nam H, Kim DU, Lee JG, Kim MS, Park JY, Park SH, Joo DJ, **Shin EC**. Identification of a distinct NK-like hepatic T-cell population activated by NKG2C in a TCR-independent manner. J Hepatol 77:1059-1070, 2022
4. Jung MK, Jeong SD, Noh JY, Kim DU, Jung S, Song JY, Jeong HW, Park SH, **Shin EC**. BNT162b2-induced memory T cells respond to the Omicron variant with preserved polyfunctionality. Nat Microbiol 7:909-917, 2022
5. Rha MS, Han JW, Koh JY, Lee HS, Kim JH, Cho K, Kim SI, Kim MS, Lee JG, Park SH, Joo DJ, Park JY, **Shin EC**. Impaired antibacterial response of liver sinusoidal $V\gamma9^{+}V\delta2^{+}$ T cells in patients with chronic liver disease. Gut 71:605-615, 2022

• April 28, 2024 (Sun) 09:00-09:15 •

HBV-Specific Tissue-Resident Memory T Cells in Human HBV-Infected Liver Diseases

Yang Cheng

Institute of Biomedical Science, Academia Sinica, Taiwan

Hepatocellular carcinoma (HCC) often develops following chronic hepatitis B virus (HBV) infection and responds poorly to immune checkpoint blockade. We examined the antigen specificities of HCC-infiltrating T cells and their relevance to tumor control. Using highly multiplexed peptide-MHC tetramer staining of unexpanded cells from blood, liver, and tumor tissues from 46 HCC patients, we screened 1,169 peptide-MHC tetramers and detected 91 different antigen-specific CD8+ T cell populations targeting HBV, neoantigen, tumor-associated, and disease-unrelated antigens. Parallel high-dimensional analysis delineated five distinct antigen-specific tissue-resident memory T (Trm) cell populations. Intratumoral and intrahepatic HBV-specific T cells were enriched for two Trm cell subsets that were PD-1loTOXlo, despite being clonally expanded. Of note, high frequencies of intratumoral terminally exhausted T cells were uncommon. Patients with tumor-infiltrating HBV-specific CD8+ Trm cells exhibited longer-term relapse-free survival. Thus, non-terminally exhausted HBV-specific CD8+ Trm cells show hallmarks of active involvement and effective antitumor response, implying that these cells could be harnessed for therapeutic purposes.

Introducing the Presenter — Yang Cheng

Education/Training

2002 – 2006 B.Sc., Soochow University, Taiwan
2011 – 2012 M.Sc., University College London, UK
2013 – 2017 P.hD., Nanyang Technological University-Singapore Immunology Network, Singapore
2017 – 2020 Postdoc, Singapore Immunology Network, Singapore

Positions and Scientific Appointments

2022 – Present Assistant Research Fellow/Principal Investigator, Institute of Biomedical Science, Academia Sinica, Taiwan
2022 – Present Adjunct Assistant Professor, National Defense Medical School, Taiwan
2020 – 2022 Senior Research Scientist, Massachusetts General Hospital/ Harvard Medical School, USA
2017 – 2020 Postdoctoral Research Fellow, Singapore Immunology Network, A*STAR, Singapore
2011 – 2012 Graduate Researcher, University College London, United Kingdom
2009 – 2011 Research Technician, La Jolla Institute for Allergy and Immunology, USA

Research Interests

His research focuses on deep-profiling human virus-specific T cells in chronic viral infection and virus-associated cancers by combining the utility of highly multiplexed combinatorial peptide-MHC (pMHC) tetramer staining and mass cytometry, high-parameter spectral flow cytometry, and single-cell multi-omics and high-dimensional modalities. Extensive experience in virus-specific T cell responses in LCMV, Hepatitis B virus (HBV) and Human papillomavirus (HPV) infection, liver cancer, head and neck cancer and autoimmune disease. He currently studies the virus-specific tissue-resident memory T cells, T cell exhaustion and TCR repertoire in the context of HBV-associated hepatocellular carcinoma, HPV-associated head and neck cancer, and SARS-CoV-2 infection and vaccination.

Publications

1. Cheng Y, Gunasegaran B, ..., Choo SP, Newell EW. Non-terminally exhausted tumor-resident memory HBV-specific T cell responses correlate with relapse-free survival in hepatocellular carcinoma. **Immunity, 2021**; (doi: 10.1016/j.immuni.2021.06.013).
2. Cheng Y, Zhu YO, Becht E, ..., Lim SG, Newell EW. Multifactorial heterogeneity of virus-specific T cells and association with the progression of human chronic hepatitis B infection. **Science Immunology, 2019**; 8;4(32):eaau6905 (doi: 10.1126/sciimmunol.aau6905).
3. Newell EW, Cheng Y. Mass cytometry: blessed with the curse of dimensionality. **Nature Immunology, 2016**; 17(8): 890-5 (doi: 10.1038/ni.3485).
4. Cheng Y, Wong MT, van der Maaten L, Newell EW. Categorical Analysis of Human T Cell Heterogeneity with One-Dimensional Soli-Expression by Nonlinear Stochastic Embedding. **The Journal of Immunology, 2016**; 196(2): 924-32 (doi: 10.4049/jimmunol.1501928).
5. Cheng Y, Newell EW. Deep Profiling Human T Cell Heterogeneity by Mass Cytometry. **Advances in Immunology**, 2016; 131: 101-34 (doi: 10.1016/bs.as.2016.02.002).

• April 28, 2024 (Sun) 09:15-09:30 •

Liver Sinusoidal T Cells in Healthy and HBV-Infected Livers

Eui-Cheol Shin

Korea Advanced Institute of Science and Technology (KAIST), Korea

The liver provides a unique niche of lymphocytes enriched with $CD8^+$ T and NK cells. To examine characteristic features of liver sinusoidal $CD8^+$ T cells, we obtained liver sinusoidal mononuclear cells from the liver perfusate of healthy donors and HBV-infected recipients during liver transplantation. First, we examined liver-enriched $CD69^+CD103^-CD8^+$ T cells. Liver sinusoidal $CD69^+CD103^-CD8^+$ T cells typically exhibited HIF-2a upregulation with a phenotype of tissue residency and terminal differentiation. $CD69^+CD103^-CD8^+$ T cells comprised non-hepatotropic virus-specific T cells as well as hepatotropic virus-specific T cells, whereas $CD69^+CD103^+CD8^+$ T cells exhibited only hepatotropic virus specificity. An HIF-2a inhibitor suppressed the effector functions and survival of $CD69^+CD103^-CD8^+$ T cells. In addition, these T cells were activated and expressed higher levels of HIF-2a in liver pathologies. In summary, we described unique characteristics of liver sinusoidal $CD8^+$ T cells in healthy and HBV-infected livers.

Introducing the Presenter

Eui-Cheol Shin

Prof. Eui-Cheol Shin received his M.D. (1996) and Ph.D. (2001) from Yonsei University College of Medicine, Seoul, Republic of Korea, and his postdoctoral training from NIDDK, National Institutes of Health, Bethesda, Maryland, USA. Then he joined Graduate School of Medical Science and Engineering, Korea Advanced Institute of Science and Technology (KAIST), Daejeon, Republic of Korea in 2007, where he is currently a professor. He is also the director of the Center for Viral Immunology, Korea Virus Research Institute, Institute for Basic Science (IBS), Daejeon, Republic of Korea, since 2021. Prof. Shin was elected as a member of The Korea Academy of Science and Technology and The National Academy of Medicine of Korea in 2019 and 2024, respectively.

Research Interests

T cell-mediated immunopathogenesis, senescence of T cells, reinvigoration of exhausted T cells, and immune responses in viral hepatitis and COVID-19

Publications

1. Kim SH, Kim J, Jung S, Noh JY, Kim J, Park H, Song YG, Peck KR, Park SH, Park MS, Ko JH, Song JY, Choi JY, Jung MK, **Shin EC**. Omicron BA.2 breakthrough infection elicits CD8+ T cell responses recognizing the spike of later Omicron subvariants. Sci Immunol 9:eade6132, 2024
2. Lee H, Jung MK, Noh JY, Park SH, Chung Y, Ha SJ, **Shin EC**. Better understanding CD8+ T cells in cancer and viral infections. Nat Immunol 24:1794-1796, 2023
3. Koh JY, Rha MS, Choi SJ, Lee HS, Han JW, Nam H, Kim DU, Lee JG, Kim MS, Park JY, Park SH, Joo DJ, **Shin EC**. Identification of a distinct NK-like hepatic T-cell population activated by NKG2C in a TCR-independent manner. J Hepatol 77:1059-1070, 2022
4. Jung MK, Jeong SD, Noh JY, Kim DU, Jung S, Song JY, Jeong HW, Park SH, **Shin EC**. BNT162b2-induced memory T cells respond to the Omicron variant with preserved polyfunctionality. Nat Microbiol 7:909-917, 2022
5. Rha MS, Han JW, Koh JY, Lee HS, Kim JH, Cho K, Kim SI, Kim MS, Lee JG, Park SH, Joo DJ, Park JY, **Shin EC**. Impaired antibacterial response of liver sinusoidal $V\gamma9^+V\delta2^+$ T cells in patients with chronic liver disease. Gut 71:605-615, 2022

• April 28, 2024 (Sun) 09:30-09:45 •

Selection of Viral Escape Mutants by CD8+ T Cells in HBeAg-Negative Chronic Hepatitis B Patients

Hung-Chih Yang

Department of Microbiology, National Taiwan University College of Medicine, Taiwan

The CD8+ T cell immunity plays an important role in suppressing the replication of hepatitis B virus (HBV) and exerts a selective pressure that shapes viral adaptation and evolution during the prolonged course of chronic hepatitis B (CHB). HBeAg seroconversion is a milestone during the natural history of CHB. Following HBeAg seroconversion, a majority of patients enter an HBV inactivation state, but a portion of them experience viral reactivation, becoming HBeAg-negative hepatitis. However, whether and how CD8+ T cell immunity and viral adaptation contribute to the dichotomous outcomes remain largely unknown. To explore this issue, we first comprehensively identified T cell epitopes of HBV presented by class I HLA (HLA-I) alleles prevalent in Taiwan using a novel platform with mass spectrometry-based immunopeptidomics and mono-allelic HLA-I cell lines. With this powerful method, we have discovered an array of T cell epitopes presented by HLA-A*11:01 and HLA-B*40:01, two of the prevalent HLA-I alleles in Taiwan. The authenticity of the epitope peptides was further confirmed by the HLA-I stabilizing assay using the TAP-I-deficient mono-allelic HLA-I cell lines. Moreover, T cell selection pressure-induced viral adaptation was determined by the HLA-I-associated viral polymorphism. We have found that HLA-A*11:01 and HLA-B*40:01-associated viral polymorphism occurred within respectively cognate T cell epitopes derived from the HBV core protein, indicating immune escape from T cell immunity. Interestingly, viral mutation escaping T cell immunity was frequently located at the anchor residue of T cell epitopes, losing its binding to cognate HLA-Is. In addition, we have also observed that viral adaptation occurred more frequently in patients with HBeAg-negative hepatitis compared to those with HBeAg-positive hepatitis and inactive HBV carriers. The HBV-specific T cell immunity is also being analyzed by the technology of multimers and flow cytometry, and the results will be presented in the meeting. In conclusion, by convincingly identifying HBV T cell epitopes, we have discovered viral escape from CD8+ T cell immunity. The occurrence of viral adaptation is more frequent among patients with HBeAg-negative hepatitis than those with HBeAg-positive hepatitis, suggesting the late-onset nature of viral adaptation after HBeAg seroconversion.

Introducing the Presenter — Hung-Chih Yang

Education

2003–2008	Ph.D., Graduate Program in Immunology, School of Medicine, Johns Hopkins University, Baltimore, Maryland, United States
1988–1995	M.D., School of Medicine, College of Medicine, National Taiwan University, Taiwan

Research and Professional Positions Held in Chronological Sequence

2023–Present	Director, Department of Microbiology, College of Medicine, National Taiwan University
2021–Present	Professor, Department of Microbiology, College of Medicine, National Taiwan University
2017–Present	Deputy Secretary General, The Gastroenterological Society of Taiwan
2010–Present	Visiting staff, Department of Internal Medicine, National Taiwan University Hospital
2017–2019	Secretary General, Taiwan Association for the Study of the Liver
2017–2018	Secretary General, Taiwan Society of Virology
2015–2021	Associate professor, Department of Microbiology, College of Medicine, National Taiwan University
2010–2015	Assistant professor, Department of Microbiology, National Taiwan University
2009–2010	Visiting staff, Department of Medical Research, National Taiwan University Hospital
2008–2009	Postdoctorate, School of Medicine, Johns Hopkins University, Baltimore, United States

Research Interests

Professor Yang's research interests lie in the T cell immune response to virus and cancer. He focuses his studies on three clinically important viruses, namely HBV, influenza virus, and SARS-CoV-2, and explore the antiviral T cell immunity. He also studies on hepatocellular carcinoma (HCC), and investigate the therapeutic potential of T cell immunity in treatment of HCC. He has published many papers in viral biomarkers, novel antiviral therapy, gene therapy, and viral immunology, including some in the high-profile journals, like Hepatology, Journal of Hepatology, and Molecular Therapy-Nucleic Acids.

Publications

1. Lin PH, Hsiao PJ, Pan CF, Liu MT, Wang JT, Ching C, Wu FY, Lin YH, Yan YC, Hsu LY, **Yang HC***, Wu UI*. 2023. Association of vaccine-specific regulatory T cells with reduced antibody response to repeated influenza vaccination. European Journal of Immunology Pub ahead , DOI: 10.1002/eji.202350525. (Co-corresponding author)
2. Cheng HR*, **Yang HC***, Lin SR, Yang TY, Lin YY, Su TH, Tseng TC, Liu CJ and Kao JH. Combined viral quasispecies diversity and hepatitis B core-related antigen predict off-nucleos(t)ide analog durability in HBeAg-negative patients. Hepatol Int. 2021 Apr 22. doi: 10.1007/s12072-021-10186-7. Online ahead of print. (co-first author)
3. Lin PH, Liang CY, Yao BY, Chen HW, Pan CF, Wu LL, Lin YH, Hsu YS, Liu YH, Chen PJ, Hu CJ* and **Yang HC***. Robust induction of TRMs by combinatorial nanoshells confers cross-strain sterilizing immunity against lethal influenza viruses. Mol Ther Methods Clin Dev 2021, 21: 299-314 (*Co-corresponding author)
4. Lin SR, Yang TY, Peng CY, Lin YY, Dai CY, Wang HY, Su TH, Tseng TC, Liu IJ, Cheng HR, Shen YC, Wu FY, Liu CJ, Chen DS, Chen PJ, **Yang HC**,* Kao JH*. Whole genome deep sequencing analysis of viral quasispecies diversity and evolution in HBeAg seroconverters. JHEP Rep. 2021 Feb 18;3(3):100254., 2021 DOI: https://doi.org/10.1016/j.jhepr.2021.100254. (*Co-corresponding author)
5. Yang YC, Chen YH, Kao JH, Ching C, Liu IJ, Wang CC, Tsai CH, Wu FY, Liu CJ, Chen PJ, Chen DS, **Yang HC**.* Permanent inactivation of HBV genomes by CRISPR/Cas9-mediated non-cleavage base editing. Mol Ther Nucleic Acids. 2020 Jun 5;20:480-490. (*Corresponding author)

• April 28, 2024 (Sun) 09:45-10:00 •

Direct Analysis of Human Hepatic Stellate Cells by Flow Cytometry

Hideki Ueno

Department of Immunology, Graduate School of Medicine, Kyoto University;
ASHBi Institute for the Advanced Study of Human Biology, Kyoto University;
Kyoto University Immunomonitoring Center (KIC), Kyoto University, Japan

Chronic hepatitis B causes liver fibrosis. Human hepatic stellate cells (HSCs) play a pivotal role by transitioning from a quiescent state (qHSC) to an activated phenotype (aHSC), which contributes to collagen deposition. Understanding the mechanisms of liver fibrosis and developing effective drugs require a thorough characterization of HSCs obtained from patients with chronic liver diseases. However, no established method exists to analyze HSCs directly from human liver tissue. We recently found that liver perfusate, obtained from healthy donor livers and chronic liver disease patients, contains HSCs. Here we show that the phenotype of HSCs can be effectively analyzed with flow cytometry (FCM), which clearly distinguishes qHSC and aHSC. Approximately 15% of aSMA+ aHSCs, but no GFAP+ qHSCs, expressed CD68 in normal donor liver perfusate. CD56 expression was also dominant by aHSCs. By contrast, CD14 was more abundantly expressed by qHSCs than aHSCs. The phenotype of HSCs was strongly altered in chronic liver diseases such as primary biliary cholangitis, and aHSCs upregulated the expression of HLA-DR, CD68, CD14, and CD40, suggesting their transformation into cells with antigen-presentation capacity. Using HSC lines established from the same patients, we found that CD40 expressed by HSC was functional and could deliver activation signals. Establishing the methods to assess the phenotype and the functions of HSCs will facilitate the studies aiming at identifying their pathological roles in human liver diseases.

Introducing the Presenter — Hideki Ueno

1992.04	**M.D.,** Kyoto University; Kyoto, Japan
2000.06	**Ph.D.,** Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan
2001-2003	**Post-Doctoral Fellow**, Baylor Institute for Immunology Research (BIIR), Dallas, TX, USA
2003-2004	**Senior Research Associate**, BIIR, Dallas, TX, USA
2004-2009	**Assistant Investigator**, BIIR, Dallas, TX, USA
2004-2016.03	**Director**, Immunomonitoring Core, BIIR, Dallas, TX, USA
2009-2011	Associate Investigator, BIIR, Dallas, TX, USA
2011-2016.03	**Investigator**, BIIR, Dallas, TX, USA
2016.04-2021	**Professor**, Department of Microbiology, Icahn School of Medicine at Mount Sinai; Global Health and Emerging Pathogens Institute, Icahn School of Medicine at Mount Sinai; New York, NY, USA
2019.07-current	**Professor**, Department of Immunology, Graduate School of Medicine, Kyoto University, Kyoto, Japan

Research Interests

- Dr. Hideki Ueno has more than 25 years of experience in human immunology research. At Baylor Immunology Research Institute, he started his research career focusing on cancer vaccine development using dendritic cells (DCs), and immunomonitoring on cancer antigen-specific T cells in patients who underwent DC-based vaccinations. He has conducted basic and clinical research on human dendritic cell subsets and human follicular helper T (Tfh) cells. Major achievements include: the determination of functional differences in human skin DC subsets; discovery of human Tfh cell subsets; elucidation of the involvement of Tfh cell subsets in autoimmune diseases; establishment of human Tfh cell differentiation pathways; and elucidation of the involvement of Tfh cells in antibody production after seasonal influenza vaccination.
- After Dr. Ueno moved to Kyoto University in 2019, he developed multiple projects covering different human immunology research topics, including human liver basic and clinical immunology studies.

Publications

1. Horiuchi S, Wu H, Liu WC, Schmitt N, Provot J, Liu Y, Bentebibel SE, Albrecht RA, Schotsaert M, Forst CV, Zhang B, **Ueno H**. Tox2 is required for the maintenance of GC TFH cells and the generation of memory TFH cells. **Sci Adv**. 2021;7(41):eabj1249.
2. Jacquemin C, Schmitt N, Contin-Bordes C, Liu Y, Narayanan P, Seneschal J, Maurouard T, Dougall D, Davizon ES, Dumortier H, Douchet I, Raffray L, Richez C, Lazaro E, Duffau P, Truchetet ME, Khoryati L, Mercie P, Couzi L, Merville P, Schaeverbeke T, Viallard JF, Pellegrin JL, Moreau JF, Muller S, Zurawski S, Coffman RL, Pascual V, **Ueno H***, Blanco P*. OX40 Ligand Contributes to Human Lupus Pathogenesis by Promoting T Follicular Helper Response. **Immunity**. 2015;42(6):1159-70. * equal contributors.
3. Schmitt N, Liu Y, Bentebibel SE, Munagala I, Bourdery L, Venuprasad K, Banchereau J, **Ueno H**. The cytokine TGF-β co-opts signaling via STAT3-STAT4 to promote the differentiation of human TFH cells. **Nat Immunol**. 2014;15(9):856-65.
4. Bentebibel SE, Lopez S, Obermoser G, Schmitt N, Mueller C, Harrod C, Flano E, Mejias A, Albrecht RA, Blankenship D, Xu H, Pascual V, Banchereau J, Garcia-Sastre A, Palucka AK, Ramilo O, **Ueno H**. Induction of ICOS+CXCR3+CXCR5+ TH cells correlates with antibody responses to influenza vaccination. **Sci Transl Med**. 2013;5(176):176ra32.
5. Morita R, Schmitt N, Bentebibel SE, Ranganathan R, Bourdery L, Zurawski G, Foucat E, Dullaers M, Oh S, Sabzghabaei N, Lavecchio EM, Punaro M, Pascual V, Banchereau J, **Ueno H**. Human blood CXCR5(+)CD4(+) T cells are counterparts of T follicular cells and contain specific subsets that differentially support antibody secretion. **Immunity**. 2011;34(1):108-21.

• April 28, 2024 (Sun) 10:00-10:15 •

Distinct NK-like Liver Sinusoidal CD56^{hi}CD8^{+}CD161^{-} T Cells Expanded in Patient with HBV Infection

June-Young Koh

Korea Advanced Institute of Science and Technology (KAIST), Inocras Inc., Korea

The liver harbors a distinct subset of lymphocytes, predominantly composed of innate-like T cells. However, the heterogeneity and functional characteristics of the hepatic T-cell population remain to be fully elucidated. We obtained liver sinusoidal mononuclear cells from the liver perfusate of healthy donors and recipients with hepatitis B virus (HBV)-associated chronic liver disease (CLD) during liver transplantation. We performed a CITE-seq analysis of liver sinusoidal CD45^{+} cells in combination with TCR-seq and flow cytometry to examine the phenotypes and functions of liver sinusoidal CD8+ T cells. We identified a distinct CD56^{hi}CD161^{-}CD8^{+} T-cell population characterized by NK-related gene expression and uniquely restricted TCR repertoire, and their frequency among the liver sinusoidal CD8^{+} T-cell population was significantly increased in patients with HBV-CLD. Although CD56^{hi}CD161^{-}CD8^{+} T cells exhibit weak responsiveness to TCR stimulation, CD56^{hi}CD161^{-}CD8^{+} T cells highly expressed various NK receptors, including CD94, KIRs, and NKG2C, and exerted NKG2C-mediated NK-like effector functions even in the absence of TCR stimulation. In addition, CD56^{hi}CD161^{-}CD8^{+} T cells highly respond to innate cytokines, such as IL-12/18 and IL-15, in the absence of TCR stimulation. In summary, the current study found a distinct CD56^{hi}CD161^{-}CD8^{+} T-cell population characterized by NK-like activation by TCR-independent NKG2C ligation. Further studies are required to elucidate the roles of liver sinusoidal CD56^{hi}CD161^{-}CD8^{+} T cells in immune responses to microbial pathogens or liver immunopathology.

Introducing the Presenter — June-Young Koh

Dr. June-Young Koh obtained his M.D. (2007) from Ulsan University College of Medicine, Republic of Korea and completed his residency training (2018) as a pediatrician at Asan Medical Center, Republic of Korea. He subsequently earned his Ph.D. (2022) in Medical Sciences with a major in Immunology from the Korea Advanced Institute of Science and Technology (KAIST). Dr. Koh serves as the Chief Research Officer at Inocras Inc., an AI-driven platform company that provides whole genome insights to enable personalized care in cancer and rare diseases from 2022. His work is recognized by several awards, including the 56th Uhan Medical Award for Young Investigators in 2023. Dr. Koh is a distinguished member of prestigious societies such as The Korean Association of Immunologists and The Korean Pediatric Society, and has made significant contributions to his fields of expertise.

Research Interests

- Systems immunology, T cell immunology, immune cell differentiation, immuno-genomics, inborn errors of Immunity (IEI), and pathologic immune response in disease status, such as IEI and viral infection.

Publications

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• April 28, 2024 (Sun) 09:00-09:15 •

Strategic direction: Alliance to Combating Vertical Transmission of Hepatitis B in Tanzania – Mobilizing Support from Asia to Africa

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Background According to the World Health Organization (WHO), approximately 1.5 million people globally are infected with HBV annually, with 95% of cases attributed to mother-to-child transmission (MTCT). While South Korea has successfully controlled its hepatitis B epidemic through robust vaccination programs, Tanzania faces a prevalence rate ranging from 3.8% to 8% among pregnant women, with 3% transmitting the infection vertically. Despite the ambitious targets outlined in the Tanzanian government's 2023 National Integrated Guideline for the Management of HIV and AIDS, Hepatitis, and Syphilis, aimed at reducing HBV MTCT to 0.1% by 2030, the practical implementation remains constrained.

Gap and Aim Tanzania's initiatives, including the introduction of a birth dose hepatitis B vaccine and the development of a protocol for MTCT prevention, have been hampered by resource constraints. This project seeks to foster collaboration between successful Hepatitis B control programs in East Asia, forming an alliance to support countries in need. The alliance will endeavor to secure external financial resources from national and international organizations to demonstrate the urgency of implementing a system for at-birth hepatitis B vaccination for newborns of HBsAg+ mothers in selected regions, alongside robust tracing programs. The objective is not only to achieve immediate success but also to advocate for policy changes and garner international support for efficient hepatitis B prevention strategies.

Specific Objectives

1. Conduct training workshops for healthcare workers on hepatitis B control.
2. Launch public awareness campaigns on at-birth hepatitis B vaccination among healthcare workers and the general population in targeted regions.
3. Establish a screening system for all pregnant women attending Antenatal Clinics in selected health facilities.
4. Implement at-birth hepatitis B vaccination for newborn to HBsAg+ mothers within 24 hours.
5. Develop an initial data management system for Hepatitis B birth dose control.

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Study Population (TBD): The study will enroll pregnant women attending Antenatal Clinics for the first time, with the endpoint being a negative HBsAg test within six months of the initial screening. Newborns of hepatitis B-positive mothers will receive their first vaccine dose at birth, followed by routine vaccination and testing at six months. Additionally, partners and family members of these mothers will be screened, and the participants' knowledge of hepatitis B infection and vaccination will be assessed.

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Introducing the Presenter

Elichilia Robert Shao

Kilimanjaro Christian Medical University College (KCMUCo), Moshi Tanzania, PhD.
Thesis: Epidemiology of Crimean-Congo Hemorrhagic Fever Virus (CCHF-V) in Tanzania, Expected graduation November 2024.
Mmed- Internal Medicine- KCMUCo, Moshi Tanzania- 2018.
Thesis: Prevalence of hepatitis B Virus infection and associated risks among healthcare workers at Kilimanjaro Christian Medical Center.
Msc- Medical Microbiology, Immunology with Molecular Biology (Major-molecular biology), KCMUCo, Moshi Tanzania- 2013.
Thesis: HIV-1 drug resistance mutations among pediatric population in Northern Tanzania.
Doctor of Medicine (MD)- KCMUCo, 2007- Moshi Tanzania.

Research Interests

Hepatitis B and C prevention and treatment, HIV pathogenesis, COVID-19 vaccination and pathogenesis, Preventive Medicine and Public health education on virology

Publications

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Poster Exhibition

• PE-01 •

Functional Region in preS1 for Forming a Stable Complex with NTCP

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Hepatitis B virus (HBV) preS1 region plays a significant role in selecting host cells and determining virion infectivity through the interaction with its entry receptor, sodium-taurocholate cotransporting polypeptide (NTCP). But the mode of preS1 recognition of NTCP has not been well clarified. In this study, we identified the functional regions involving in preS1 that recognized the substructure of NTCP and their significance in productive infection.

In the structure of preS1 (2–48 aa)-NTCP complex recently solved (Asami et al. Nat Struct Mol Biol 2024), preS1 contacts with the bile acid tunnel through the first loop (loop A: 7–19 aa) along with transmembrane (TM)5 and the second loop (loop B: 20–32 aa) between TM1 and TM5, with additional contacts of C-terminal extension (33–48 aa) to the extracellular surface of NTCP at the end of TM8b. We then prepared the peptide consisting of these preS1 subregions, myr-2–19^{preS1}, 20–32^{preS1}, and 33–48^{preS1} to assess the activity of NTCP binding and competition to virus infection. Fluorescence-labeled 20–32^{preS1} and 33–48^{preS1} peptide did not show affinity to HepG2-NTCP cells at any treated concentrations, whereas myr-2–19^{preS1} showed the dose-dependent binding to HepG2-NTCP cells, but its binding was much less than myr-2–48^{preS1}. Consistently, 20–32^{preS1} and 33–48^{preS1} had no competition activity to inhibit hepatitis D virus (HDV) infection, but 2–19^{preS1} inhibited infection with 50% inhibitory concentration (IC_{50}) of 56.2 nM, which was less active than myr-2–48^{preS1} (IC_{50}=3.8 nM). These data suggested that 2–19^{preS1} is essential for establishing the NTCP binding, but further C-terminal region enhance the affinity to NTCP. We also showed amino acid substitutions within 2–19 aa that completely abrogated the NTCP binding activity.

These results provide information useful for developing anti-HBV/HDV drugs and for understanding the high affinity host recognition of these viruses.

• PE-02 •

Inhibitory Activity of Sterol Derivatives against HBV Entry and Its Mechanism

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Epidermal growth factor receptor (EGFR) mediates the internalization of hepatitis B virus through binding to its receptor, sodium taurocholate cotransporting polypeptide (NTCP) (Iwamoto et al., PNAS, 2019). To explore whether NTCP-EGFR interaction can serve as a new drug target, we identified compounds inhibiting this interaction and analyzed their anti-HBV activity. We established an in vitro AlphaScreen assay that evaluated the NTCP-EGFR interaction and screened 1000 small molecule-based and peptide-based compounds. Effect of compounds on HBV infection was examined in HepG2-NTCP cell-based HBV infection assay.

The processes for replication and viral attachment were evaluated using an HBV-tet-off cell line and HepG2-NTCP cells exposed with a TAMRA-labelled preS1 peptide (preS1-TAMRA), respectively. Internalization of preS1-TAMRA was evaluated by confocal microscopy. EGFR downstream signalings were assessed by immunoblot with phospho-antibodies against EGFR, Akt, and Erk. From a compound screening, we identified #229, a sterol derivative, which specifically reduced the AlphaScreen signal produced by NTCP-EGFR interaction. #229 inhibited HBV infection to HepG2-NTCP cells in a dose dependent manner without significant cytotoxic effect. #229 affected neither HBV replication induced by tetracycline depletion nor preS1-TAMRA attachment of HepG2-NTCP cells. In contrast, internalization of preS1-TAMRA along with the time course after cell surface attachment was significantly blocked upon #229 treatment. Interestingly, #229 did not affect the downstream signaling of EGFR including the phosphorylation of Akt and Erk, which was completely inhibited by gefitinib. We further identified derivatives of this compound having more potent and HBV activity. Thus, our study suggest that NTCP-EGFR interaction will serve as a new target of the development of anti-HBV agent.

• PE-03 •

Development of a Novel Liver-Immune Organoid Model to Reproduce the HBV Infected Liver Microenvironment

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In Human hepatitis B virus (HBV)-infected patients, achieving functional cure by producing hepatitis B surface antibody (HBsAb) is important to reduce the incidence of liver cirrhosis and cancer. Since the probability of spontaneous HBsAb seroconversion is reported to be only 1-3%, the development of treatments to induce the production of HBsAb is desired. While primary human hepatocytes (PHHs) have been a major cell source to study HBV infection for its limitation of susceptible species, PHHs are difficult to expand and maintain for a long period of time in vitro. To overcome those problems, we developed primary human liver derived organoid model from liver biopsy tissue of healthy donors in liver transplantation, which can infect with HBV and culture for long period of time. First, we successfully created liver organoids derived from primary EpCAM positive cells which can expand under the optimized culture condition, whereas PHHs rarely proliferate in vitro culture condition. We also confirmed that the organoid cells can differentiate into hepatocyte-like cells expressing NTCP and can be infected with HBV. Finally, the organoid cells are cocultured with intrahepatic immune cells from the same HBsAb negative donor to reproduce the immune microenvironment in liver under HBV infection. Using this coculture model, we analyzed how HBV infection affects intrahepatic immune cell phenotypes particularly focusing on antigen-presenting cells. Interestingly, we found no significant changes in intrahepatic immune cells by flow cytometry after 2-day-coculture experiments. These results reflect low immunogenicity of HBV in this autologous liver-immune organoid model. Further analysis is needed to reveal the mechanism how HBV specific immune responses occur and lead to HBs seroconversion.

• PE-04 •

Mapping of Amino Acid Region in NTCP Involved in the Interaction with HBV preS1

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Hepatitis B virus (HBV) infection is initiated by binding of its preS1 region of the viral envelope protein to the host entry receptor, sodium taurocholate co-transporting polypeptide (NTCP). However, the detailed preS1 recognition mechanism by NTCP is poorly clarified. In this study, we identified the amino acid site/structure in NTCP involved in the binding to preS1.

Based on the recently identified structure of NTCP/preS1 complex (Asami et al. Nat Struct Mol Biol 2024), we selected 56 amino acids in NTCP that closely contacted with preS1 resided within 4.5 Å. We produced 112 NTCP variants having a mutation in these selected amino acids to alanine or tryptophan. These mutants were overexpressed in HepG2 cells and were tested for binding to a fluorescence-labeled preS1 peptide, HBV infection, uptake of [3H]-taurocholic acid, as well as cell surface expression levels.

Besides the previously reported essential amino acids such as Asn87, Gly158, and Ser267, our mutation analysis identified amino acid substitutions that altered preS1 binding levels, especially at transmembrane 1 and 5 that faces the bile acid tunnel and the extracellular surface of NTCP. We are now underway to identify the amino acids selectively involved in preS1 binding and HBV infection but not bile acid uptake.

These information are useful for understanding the molecular mechanism underlying HBV-receptor binding and for identifying the target that enables the specific inhibition of HBV infection with securing the original function of NTCP.

• PE-05 •

Role of Lipid Droplet Accumulation in HBV-HCC Development

Ryuta Ueda

National Institute of Infectious Diseases, Japan

Liver carcinogenesis by chronic hepatitis B infection involves multiple events including viral gene expression, host gene mutation, integration into the host genome, and altered host gene expression. However, their associations with each other have not been verified in detail.

In this study, we analyzed 10 surrounding tissues of hepatocellular carcinoma developed from chronic hepatitis B (HBV-HCC), as well as 27 chronic hepatitis B without diagnosis of HCC.

Focusing on lipid droplet accumulation found by electron microscopy, we found its association with viral gene expression, host gene mutations with specific signatures, and viral integration, in the surrounding tissues, but not in the CHB cases. How these events induce each other and contribute to HBV-HCC development will be discussed.

• PE-06 •

Decreased Risk of Hepatocellular Carcinoma in Patients with Chronic Hepatitis B Treated with Besifovir

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Background/Aims: Besifovir dipivoxil maleate (BSV) is a new potent antiviral agent approved in Korea. The favorable antiviral effect of BSV may lower the risk of HCC in patients with CHB. Nevertheless, there is currently a lack of information concerning the impact of BSV treatment on the occurrence of HCC. We aimed to assess the incidence of HCC under BSV therapy using clinical trial and real-world BSV data and to compare it with that observed during entecavir (ETV) or tenofovir disoproxil fumarate (TDF) therapy.

Patients and Methods: We combined the phase 3 clinical trial data of BSV which was conducted for 8 years and retrospective data which was collected in the real-world. The retrospective cohort consisted of patients who initiated ETV, TDF, or BSV as a first treatment between 2007 and 2022 at five tertiary hospitals. Incidences of HCC under these antiviral therapies were compared. To further validate, we conducted propensity score matching with an optimal variable ratio of 1:2 or 1:1 for the ETV or TDF treatment groups, respectively. This approach allowed us to create matched cohorts and enabled a more meaningful comparison of HCC incidences between the groups. We performed the log-rank test to evaluate any significant differences.

Results: A total of 385, 1139, and 688 patients were treated with BSV, ETV, and TDF, respectively. The

incidence of HCC was significantly lower in the BSV group compared with ETV or TDF groups (BSV vs ETV, *P* = 0.007; BSV vs. TDF, *P* = 0.015).

After propensity score matching, we observed that the incidence rate of HCC remained significantly lower in the BSV group in comparison to the ETV group (*P* = 0.016). However, there was no significant difference in HCC incidence rates between the BSV and TDF groups (*P* = 0.253). Further analysis using multivariable analysis within this matched cohort indicated that BSV significantly reduced the risk of developing HCC when compared to ETV.

Conclusions: BSV therapy may improve prognosis of patients with CHB by decreasing the incidence of HCC.

• PE-07 •

Effects of Tenofovir Disoproxil Fumarate versus Tenofovir Alafenamide on Risk of Osteoporotic Fracture in Patients with Chronic Hepatitis B

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As tenofovir disoproxil fumarate (TDF) necessitates long-term use, the possibility of reduced bone density should be considered when treating patients with chronic hepatitis B (CHB), particularly with advancing age and systemic diseases. Patients treated with tenofovir alafenamide (TAF) exhibit improved bone mineral density compared to those treated with TDF. Despite reported enhancements in bone density with TAF, no study has assessed the disparity in osteoporotic fracture risk between TAF and TDF treatment in CHB patients in real-world practice. Therefore, our objective was to evaluate the impact of TAF on the risk of osteoporotic fractures compared to that of TDF.

Utilizing national claims data from the Health Insurance Review and Assessment Service, we conducted a retrospective cohort study involving 32,582 patients with CHB who were initially treated with either TDF or TAF between November 2017 and December 2020. Of these, 20,877 patients received TDF while 11,705 received TAF. The annual fracture rate per 100 patients in each group was calculated, and Cox proportional hazard ratio (HR) analysis was performed after applying inverse probability treatment weights (IPTW) for both groups.

Among the 32,582 patients, the average age was 47.8 ± 11.2 years, 64.5% were men, and the follow-up period was 24.4 ± 11.6 months. TDF was more commonly prescribed to patients with diabetes mellitus ($p < 0.001$) and corticosteroids ($p < 0.001$), while other comorbidities were similar between the two groups. Over 66,145 person-years of follow-up, the incidence of osteoporotic fractures was 0.78 and 0.49 per 100 person-years in the TDF and TAF groups, respectively. After the application of IPTW, the HR was 0.68 (95% confidence interval 0.55–0.85, $p = 0.001$). The association pattern between treatment and osteoporotic fractures remained consistent across subgroups, and there were no significant differences in fracture sites between the two groups.

In conclusion, patients with CHB treated with TAF had a significantly lower risk of osteoporotic fractures compared to those treated with TDF.

• PE-08 •

Strong Cross-Neutralizing Antibodies Induced by a Hybrid Large Hepatitis B Surface Protein Composed of Two Viral Genotypes C and D

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Background: Hepatitis B virus (HBV) vaccination is known to effectively decrease the risk of HBV infection. However, several issues need to be addressed in order to develop an improved HBV vaccine. Although the HBV vaccine has been shown to be effective, this vaccine needs to be more efficacious in defined groups, including non-responders (i.e., individuals who do not develop a protective response even after vaccination) and in health care workers and travelers who require rapid protection. Furthermore, it has been reported that universal HBV vaccination has accelerated the appearance of vaccine-escape mutants resulting from the accumulation of mutations altering the "a" determinant of the hepatitis B surface (SHBs) protein.

Method: To address these problems, we have been focusing on the large HBs (LHBs) protein, which consists of three domains: pre-S1, pre-S2, and S (in N- to C-terminal order). To enhance the immunogenicity of LHBs, we developed a yeast-derived hybrid LHBs (hy-LHBs) antigen composed of the LHBs proteins from two distinct genotypes (Genotypes C and D).

Results: The levels of antibodies induced by hy-LHBs immunization were high not only against S, but also against the pre-S1 and pre-S2 domains. Among HBs proteins, hy-LHBs induced the highest neutralizing antibody titer against all genotypes of HBV tested in this study, and all mice immunized with hy-LHBs were neutralizing antibody-positive against all genotypes of HBV. In contrast, some mice immunized with SHBs or LHBs were neutralizing antibody-negative, even after three immunization injections. Immunization with hy-LHBs induced strongly cross-reactive neutralizing antibodies against not only HBV of Genotypes C and D, but also those of Genotypes A and B.

Conclusion: Immunization with hy-LHBs antigen strongly induced antibodies against all three HBs domains, including pre-S1, pre-S2 and S. The antibodies induced by hy-LHBs immunization demonstrated strongly cross-reactive neutralization activity. Together, these findings indicate that hy-LHBs may serve as a candidate component for incorporation into a prophylactic HBV vaccine.

• PE-09 •

Impact of Alpha-Fetoprotein Expression on Interferon Pathways and VEGFA in Hepatocellular Carcinoma Microenvironment after Hepatitis C Virus Eradication

Katsuya Nagaoka

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Background: Alpha fetoprotein (AFP) is a serum protein found in fetuses during early pregnancy and has been used as a tumor marker for hepatocellular carcinoma (HCC). Serum AFP levels are often elevated in chronic hepatitis B and C, even in the absence of HCC. In fact, we have reported that even slightly elevated AFP levels in the range of less than 20 ng/mL are a risk factor for liver carcinogenesis in chronic liver disease (J Gastroenterol. 2011; 46: 92.). Thus, AFP expression increases with hepatitis and tumor growth, but conversely, it is not well understood whether AFP expression affects the cellular environment in hepatocarcinogenesis.

Methods & Results: In vitro experiments utilized hepatocarcinoma-derived cells (HepG2) and normal hepatocyte-like cells (HuSE) with an AFP overexpressing system. Comprehensive analysis of differentially expressed genes in AFP-expressing cell lines and bioinformatics analysis by Gene Set Enrichment Analysis (GSEA) revealed significant associations between AFP expression and interferon-α /γ, as well as genes related to fatty acid metabolism. Examining liver resection specimens from patients who developed HCC post-Sustained Virological Response (SVR) showed a consistent positive correlation between AFP gene expression and interferon-α-related genes in cancerous and non-cancerous areas. Additionally, VEGFA gene expression was strongly correlated with these genes in cancer regions. These findings suggest that even slight increases in AFP expression (below 20 ng/ml) may influence the hepatocellular carcinoma microenvironment, impacting interferon-α-related pathways and VEGFA gene expression.

Conclusions: The study emphasizes the potential significance of AFP in understanding the cellular environment during hepatocarcinogenesis after Hepatitis C virus eradication.