Cancer Virology Program Spring Newsletter

Published: February 24th, 2023

Program Overview

Fast forward, the Winter is almost behind us, and the signs of Spring are already everywhere, and we are almost in March! As always, all the CVP labs are busy with their exciting discoveries and innovative works irrespective which season we are in. Under the leadership of Dr. Robert Ferris, the UPMC Hillman Cancer Center celebrated the grand opening of The Assembly Building last summer and many laboratories and facilities have since transitioned into the new building. CVP has also taken advantage of the new facilities and continued to host the biweekly working progress (WIP) seminars in The Assembly Suite B1610.

Cancer Virology Program

CVP welcomed its newest member: Dr. Renfeng Li, who was a tenured Associate Professor at Virginia Commonwealth University (VCU), and officially joined CVP on January 1st, 2023 as a tenured Associate Professor in the Department of Microbiology and Molecular Genetics. We have highlighted his research in this issue, in which you can learn about his exciting research program.

Numerous labs have published their new exciting scientific findings since the publication of the last Newsletter. Due to space limitations, we have only highlighted a few of them but you can check out the rest by reading their published articles listed toward the end of this issue.

Since we restarted the WIP seminars at the end of the summer, after the declaration of "the end of COVID-19", it has evolved into a routine and favorite program activity, in which students, Postdoctoral Fellows and Faculty Members enjoy presenting and sharing their works. It has become a great venue to learn what is going on in other labs in the program and establish both intra- and inter-programmatic collaborations. Please check out the lists in this issue for both past and upcoming presentations.

In addition to the WIPs, CVP has hosted numerous outstanding speakers whose topics encompassed a variety of cancer viruses including HPV, KSHV and EBV. We will host several other excellent speakers in the Spring and early Summer. This includes Dr. David Knipe, an Academy Member of the National Academy of Science, and the Higgins Professor of Microbiology and Molecular Genetics, and Head of the Harvard Program in Virology at the Department of Microbiology, Blavatnik Institute, at Harvard Medical School. Dr. Knipe will present his seminar on April 11, 2023. In collaboration with the Community Outreach and Engagement (COE), CVP is planning a symposium that will occur on October 10th, 2023, in which we will host Keynote Speaker Dr. Charles Rice from Rockefeller University, who is a Nobel Laureate. Symposium program is to be announced. Please mark your calendar.

Edited by Dr. Shou-Jiang Gao

Inside This Issue:

Contact Us:

For more information on the Cancer Virology Program, please contact the CVP Program Leaders:

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- Dr. Haitao Guo: guoh4@upmc.edu

Program Member Highlights

Dr. Renfeng Li

Dr. Li is a Member of the UPMC Cancer Virology Program (CVP) and an Associate Professor in the Department of Microbiology & Molecular Genetics. He obtained a B.E. in Analytical Chemistry from Beijing University of Chemical Technology, Beijing, China, and a Ph.D. in Biology for Tsinghua University, Beijing, China where he studied SMAD1 and its E3 ubiquitin ligase CHIP in bone morphogenic protein (BMP) signaling pathway.

Before joining Pitt in 2023, Dr. Li was a tenured Associate Professor at Virginia Commonwealth University (VCU). His laboratory is focused on understanding the mechanism controlling Epstein-Barr virus (EBV) latency and reactivation with a long-term goal of developing novel strategies to cure virus-associated diseases. In the past eight years, Dr. Li's laboratory has been focusing on host restriction factors in herpesvirus replication and the viral evasion mechanisms, which results in a series of high-profile publications in PLOS Pathogens (2015 and 2018), Cell Reports (2017 and 2019) and mBio (2021). Dr. Li has also been awarded several highly completive grants from NIH (K99/R00 and R01) and the American Cancer Society (ACS Research Scholar).

Dr. Li's lab has established multiple cell model systems to address EBV latency and reactivation in both B cells and epithelial cells. His group identified PIAS1 as a key regulator of EBV lytic replication and uncovered a novel mechanism by which EBV exploits apoptotic caspases to antagonize PIAS1-mediated restriction (Zhang et al, Cell Reports 2017). Based on this work, Dr. Li also received an EBV & Kaposi's Sarcoma associated herpesvirus (KSHV) Scholarship Award provided by the International Conference on EBV & KSHV in 2018.

Prior joining VCU in 2014, Dr. Li was a Postdoc Fellow at Johns Hopkins University School of Medicine under the mentorship of renowned herpesvirologist Dr. Diane Hayward. He later was co-mentored by a world leader in quantitative mass spectrometry (MS), Dr. Akhelish Pandey, with NIH K99 training award.

The discovery of restriction factor cleavage highlighted an important role of apoptotic caspase in tumor virus replication and, subsequently, promoted by his own lab and other groups to further investigate the key role of caspase activation in EBV, KSHV and human papilloma virus (HPV) infections. Using his extensive expertise in both virology and proteomics, Dr. Li and group members are utilizing an innovative immunoprecipitation coupled with quantitative MS approach to monitor protein cleavage in EBV-positive Burkitt lymphoma cells upon lytic induction. Among more than 1,000 proteins that they identified as caspase substates during EBV replication, they are focusing on hnRNPA2B1 and PRC1 complex protein RING1 for further functional analysis.

Dr. Li is very active and successful in training Post-doctoral Fellows and graduate students. One of the former Postdoc Fellows, Dr. Kun Zhang, received multiple travel awards, including a prestigious David Baltimore Fellowship Award from American Society for Virology (ASV). Another Postdoc Fellow, Dr. Saiada Farjana, also won several awards, including Research presentation Award at VCU and Travel Award by ASV. The Ph.D. student, Febri Gunawan Sugiokto, joined the lab in 2021 and won four awards for his reach done in the Li lab, including VCU Research Day Presentation Award, and merit-based Travel Awards by ASV and International Herpesvirus Symposium (IHW) and more recently, Travel Award provided by Chromatin Control of Viral Infection Workshop (CCVI).

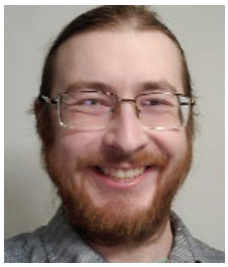
Dr. Li's service to the broader virology and cell biology research community is notable. Dr. Li is the current President for the Association of Chinese Virologist in America (ACVA) and the Society of Chinese Bioscientists in America (SCBA)-Virology Division (2023-2024). He serves as the Advisory Board Member and Webmaster for ACVA/SCBA-Virology Division (2018-present). He also serves as the membership committee member and webmaster for SCBA. In the past, he served as the session chair for Chromatin Control of Viral Infection Workshop (CCVI) in 2018 and 2022. He served as the webmaster and program organizer for the 18th SCBA International Symposium held in Boston in 2022. Dr. Li is the Editorial Board member for Journal of Virology and Viruses.

New Lab Members

Xiao Peng

Xiao Peng, a Tsinghua-Pitt scholar, joined the Guo lab in September 2022 to conduct his 2-year biomedical research.

Dr. Joshua Walston, Ph.D.



Dr. Walston joined Dr. Kathy Shair's lab on Feb 1, 2023 as a Postdoctoral Fellow. Dr. Walston received his Ph.D. in Biomedical Sciences in Virology and Immunology from Penn State University College of Medicine, from the laboratory of Dr. Clare Sample. He is an expert on organotypic rafts, and his dissertation examined the role of EBV glycoproteins BDLF2 and BMRF2 in infection and spread in the oral epithelium. He will work on nasopharyngeal 3-D cultures and examine sequence variants of EBV LMP1 in differentiation-dependent lytic infection.

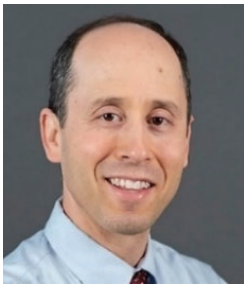
Program Activities

CVP has hosted several visitors and invited speakers this past fall. Each of them presented a seminar either at UPMC Hillman Cancer Center or the Department of Microbiology and Molecular Genetics as well as meeting with several faculty and staff during their visits.

Javier Gordon Ogembo, Ph.D.

Dr. Ogembo is an Associate Professor Department of Immuno-Oncology at Beckman Research Institute of City of Hope in Duarte, CA. He was invited through the CVP and visited us on September 12-13, 2022. He presented a seminar entitled*: "A Historical Perspective of Human Oncogenic Herpesviruses and the Quest for a Protective Vaccine"* at UPMC Hillman Cancer Center. *(Host: Dr. Shou-Jiang Gao)*

Benjamin Gewurz, M.D., Ph.D.



Dr. Gewurz is the Associate Chair at Harvard Graduate Program in Virology and an Associate Professor and Physician at Brigham and Women's Hospital and Harvard Medical School. He was invited through the Department of Microbiology and Molecular Genetics and visited us on September 21, 2022. He presented a seminar entitled*: "Metabolism Controls the B cell EBV Epigenome and Viral Latency"* at Bridgeside Point II. *(Host: Dr. Shou-Jiang Gao)*

Christopher Sullivan, Ph.D.

Dr. Sullivan is a Professor of Molecular Biosciences at the University of Texas at Austin. He was invited through the CVP and visited us on October 3-4, 2022. He presented a seminar entitled: *"Noncoding RNA and Triphosphate Balance in Virus Infection"* at UPMC Hillman Cancer Center. *(Host: Dr. Shou-Jiang Gao)*

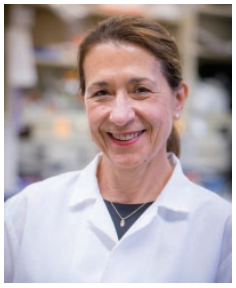
Elizabeth White, Ph.D.

Dr. White is an Assistant Professor in the Departments of Otorhinolaryngology and Microbiology at the University of Pennsylvania Perelman School of Medicine. She was invited through the CVP and visited us on November 14-15, 2022 and presented a seminar entitled: *"Mechanisms of Human Papillomavirus Persistence and Epithelial Carcinogenesis"* at UPMC Hillman Cancer Center. *(Host: Dr. Shou-Jiang Gao)*

Cary Moody, Ph.D.

Dr. Moody is an Associate Professor in the Department of Microbiology and Immunology at the Lineberger Comprehensive Cancer Center at the University of North Carolina at Chapel Hill. She was invited through the CVP and visited us on December 5-6, 2022. She presented a seminar entitled: *"Virus: Host Interactions that Regulate the Replication of Human Papillomaviruses"* at UPMC Hillman Cancer Center. *(Host: Dr. Shou-Jiang Gao)*

Ourania Andrisani, Ph.D.



Dr. Andrisani is the Distinguished Professor in Department of Basic Medical Sciences, Purdue University, and the Co-Leader of Cell Identity and Signaling Program, Purdue Institute for Cancer Research. Dr. Andrisani was invited through Pittsburgh Liver Research Center (PLRC) and visited us on January 23-24. She presented a seminar entitled "RNA helicase DDX5 in Hepatitis B virus biosynthesis and hepatocellular carcinoma" in PLRC. *(Host: Dr. Haitao Guo)*

Recent CVP "Work In Progress" Presentations

Wen Meng - 10/21/22: "METTL16-Specific N6-Methyladenosine (m6A) Regulation of One Carbon Metabolism and Oxidative Stress in Oncogenic KSHV Replication"

Xiaoyang Yu - 11/4/22: "Interferon stimulated gene 12 (ISG12/IFI27) inhibits HBV transcription through downregulating transcription factor C/EBPα"

Elena S. Kim - 11/18/22: "Hepatitis B virus X protein counteracts high mobility group box 1 protein-mediated epigenetic silencing of covalently closed circular DNA"

Benjamin E. Warner - 12/2/22: "Liquid biopsy for cancer prevention: Can Epstein-Barr virus serology assess nasopharyngeal carcinoma risk?"

Zandrea Ambrose - 12/16/22: "Don't You Forget about M & E: Understanding the Role of the Other SARS-CoV-2 Structural Proteins on Infectivity"

Chandra Nath Roy - 1/6/23: "Development of a Humanized Mouse Model for HIV-1 Transmission and Pathogenesis"

Neal DeLuca - 1/20/23: "Transcription of the HSV genome: Accessibility and Recruitment"

Sumin Jo - 2/3/23: "Study of Intrinsic m6A Sites"

Zac Ingram - 2/17/23: "Characterizing Sequential Host Factor Binding to HIV-1 Capsid using a Unique Mutant"

Newly Funded

Dr. Terence Dermody

1R01AI174526-01, 09/22/22-07/31/27, total cost: $565,478.00 entitled: ***"Reovirus Neuropathogenesis" (Linked here).*** The proposed research will enable a better understanding of mechanisms used by viruses to infect specific CNS regions and spread within neurons to disseminate in the brain. This information will be useful for the identification of new drug targets for the treatment of viral encephalitis and the development of precision-guided oncolytic vectors to treat nervous system cancers.

Dr. James Conway

1R01 AI175067-01, 09/19/22-07/31/27, total cost: $18,945.00 entitled: ***"'On the Fly' Time Resolved Cryo-EM Studies of Intermediate HIV-1 RT Transition States" (Linked here).*** Our group has developed cutting-edge technology - "on-the-fly" time-resolved cryo-electron microscopy (EM) - that, for the first time, facilitates visualization of novel protein conformations, including those transiently occurring during catalysis. In this application, we will apply this technology to address biologically and clinically relevant knowledge gaps in HIV-1 reverse transcriptase (RT) biology, with specific focus on the incorporation of nucleosides and nucleoside inhibitors, nucleoside inhibitor resistance, and the relationship between DNA synthesis and ribonuclease H activity.

1R01GM144981-01, 09/23/22-08/31/26, total cost: $459,613.00 entitled**:** ***"Structure and assembly of dsDNA tailed bacteriophages" (Linked here).*** Viruses that infect bacteria – bacteriophages – are exceptionally numerous, and the largest structural family has deep and important connection with human herpesviruses, an important pathogen for which no effective long-term remedies are available. They have potential for use as antibiotics and in drug and vaccine development. Our study aims to understand the organization and functions of the virus proteins required for assembly and that incorporate the viral genome. This knowledge will form a framework for understanding the structure and assembly of this large virus family and will inform the development of therapeutic approaches.

Dr. Moses Bility

1R01 AI162615-01A1, 08/02/22-07/31/26, total cost: $193,389.00 entitled: ***"Elucidating the role of B cell mediated trans infection in the establishment of the latent HIV-1 reservoir" (Linked here).*** HIV-1 trans-infection is thought to play a key role in the pathogenesis of HIV-1 infection. Direct evidence of HIV- 1 trans-infection in vivo, however, is lacking. In this this application, we propose to use novel state-of the-art approaches to ascertain whether B lymphocyte-mediated cell-to-cell HIV-1 trans-infection contributes to the establishment and replenishment of the latent viral reservoir in resting CD4+ T cells. We anticipate that this study will provide the first in vivo evidence that HIV-1 trans-infection plays a key role in viral pathogenesis.

Dr. Angela Gronenborn

1U54AI170791-01, 07/01/22-04/30/27, total cost: $968,721.00 entitled: ***"NMR Core" (Linked here).*** The overall goal of the NMR Core is to provide state-of-the art capabilities for PCHPI researchers, for atomic-level characterization of structure and dynamics of HIV-1 proteins and their complexes. To accomplish this goal, we will take advantage of superb instrumentation resources, innovative experimental protocols, and unique expertise developed during the past decade. Specific aims are designed to i) support PCHPI projects and extra- center collaborators by providing cutting-edge solid-state NMR capabilities for HIV-1 research, and ii) develop in-cell solution and solid state 19F NMR for HIV-1 research. The novel technologies developed by the NMR Core will have major impact on HIV-1 cellular structural biology.

Dr. Zandrea Ambrose

1R21 AI167710-01A1, 06/01/22-05/31/23, total cost: $37,070.00 entitled: ***"Evaluating macrophage antiviral immunity as a suppressive factor in SIV-M. tuberculosis co-infection" (Linked here).*** Individuals with HIV-M. tuberculosis coinfection are at severe risk of tuberculosis (TB). The basis for this susceptibility is not known but may be driven a shift away from macrophage antibacterial immunity towards antiviral responses. This project uses high-dimensional imaging and analysis in combination with innovative mechanism-level in vitro studies to identify how viral infection compromises immunity in TB.

1U54AI170791-01, 07/01/22-04/30/27, total cost: $741,975.00 entitled: ***"Project 2. Immune evasion, trafficking, and nuclear import" (Linked here).*** Immune evasion, trafficking and nuclear import The HIV-1 capsid acts as the primary interface between the virus and the cell during viral ingress and nuclear entry. The capsid is critically involved throughout all steps of the replication cycle, including uncoating, recognition by host factors, trafficking along microtubules, nuclear import, and genome integration. Recent research revealed that HIV-1 capsid hijacks microtubule motors dynein and kinesin for its journey towards the nucleus, and an intact capsid can traverse the cellular nuclear pore complex (NPC). These data significantly impact our views of HIV-1 cytoplasmic transport, nuclear import, intranuclear transport, and uncoating, and indicate that capsid is a key player in HIV-1 ingress. However, atomic-level understanding of capsid recognition by host factors is lacking, and it is unclear how the dynamic exchange of factors occurs during viral movement from the cell periphery to the site of integration inside the nucleus. The overall goal of this project is to fill these knowledge gaps by providing critical structural and dynamic information on capsid's engagement in immune evasion, trafficking and integration.

Dr. John Mellors

Case Western Reserve University: (XXX419281XXX, 05/01/22-04/30/27, total cost: $140,456.00) entitled: ***"Case/UHC-Pitt Center for AIDS Research (Rustbelt CFAR)."***

Awards & Honors

Fellowship Awarded

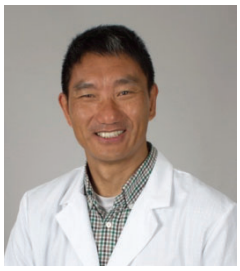
Dr. Arun Das, a Postdoctoral Associate from Dr. Yufei Huang's lab has been awarded a Hillman Postdoctoral Fellowship for Innovative Cancer Research. Congratulations are most surely in order for this significant accomplishment.

Dr. Benjamin Warner, Ph.D.

Dr. Warner received the Hillman Postdoctoral Fellows award for Innovative Cancer Research. He is co-mentored by Dr. Kathy Shair and Dr. Jian-Min Yuan. On this project, he will continue to use liquid biopsy to refine serological assays to identify biomarkers for the risk assessment of nasopharyngeal carcinoma and EBV-associated malignancies. This career development award is for a 2-year period and is intended to give postdocs the mentorship support and funds to submit a competitive K99/R00 application. Congratulations to Dr. Warner on this fine achievement!

Dr. Haitao Guo

Dr. Guo's oral presentation entitled ***"High levels of intrahepatic integrated HBV DNA that correlated with serum quantitative HBsAg level in HBeAg negative chronic hepatitis B"*** was selected as *"Best of The Liver Meeting"* by 2022 AASLD Meeting. Congratulations on this honor!



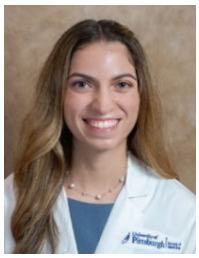
Dr. Shou-Jiang (SJ) Gao

Dr. Gao was invited to give an expert seminar entitled: **"Function of novel tumor suppressor CASTOR1 in cancer and inflammation"** for the Center of Infectious Diseases and Pathogen Biology, Jilin University on November 30, 2022 (Virtual).

Dr. Gao was invited to give a seminar entitled: **"Arginine sensor CASTOR1 as a tumor suppressor in viral and nonviral cancers and in inflammation"** at the McArdle Laboratory for Cancer Research, University of Wisconsin-Madison, Madison, WI on November 2, 2022.

Dr. Masahiro (Masa) Shuda

Dr. Shuda was invited to present his research ***"Merkel Cell Polyomavirus Persistence and Merkel Cell Carcinoma"*** in the Microbiology Seminar Series in University of Pennsylvania Perelman School of Medicine on May 11, 2022.



Shiva Yagobian

Shiva, a Pitt medical school student in Dr. Masa Shuda's lab (Class of 2026) was elected for the Pitt-Med Research Experience for Pre-matriculants (PREP) program. She also received a travel award to present at the Midwest HPV and Polyomavirus Symposium.

Michelle Khattri

Michelle, a Pitt undergraduate student in Dr. Masa Shuda's lab (Class of 2023) received the 2022 Chancellor's Undergraduate Research Fellowship (CURF). Congratulations on your research fellowship!

In the News

Interview with Dr. Kathy Shair

Dr. Shair was recently interviewed by ***"Researcher"*** on the research article ***"A primary nasopharyngeal three-dimensional air-liquid interface cell culture model of the pseudostratified epithelium reveals differential donor- and cell type-specific susceptibility to Epstein-Barr virus infection."*** Click here to listen to or read the interview and click here to read the article.

Dr. Patrick Moore Completes Review Synthesis

Dr. Moore was responsible for synthesizing an NCI-sponsored review on prospects for the development of a KSHV anti-cancer vaccine based on an expert working group review. This activity has led to a joint publication with all participants: Casper C, Corey L, Cohen JI, Damania B, Gershon AA, Kaslow DC, Krug LT, Martin J, Mbulaiteye SM, Mocarski ES, **Moore PS**, Ogembo JG, Phipps W, Whitby D, Wood C. KSHV (HHV8) vaccine: promises and potential pitfalls for a new anti-cancer vaccine. NPJ Vaccines. 2022;7(1):108.

Dr. Haitao Guo Honors

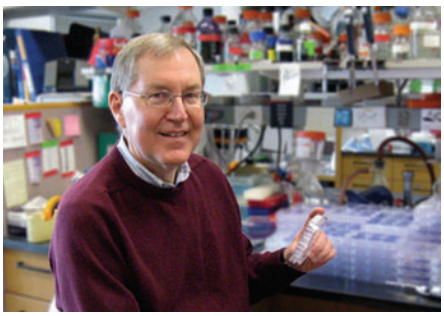
Dr. Guo is co-editing a book: ***"Methods in Molecular Biology-HBV (2nd Edition),"*** which will be published by Springer in the Fall of 2023. He has also been appointed the **Deputy Editor of Journal of Medical Virology**, starting January 1, 2023. Congratulations on your appointment.

Funding From NIH is Up!

The University of Pittsburgh moved from 11th to 3rd in NIH funding in 2022. Read more by clicking here.

Upcoming Events

David M. Knipe, Ph.D. - April 11



Dr. David Knipe, an Academy Member of the National Academy of Science, and the Higgins Professor of Microbiology and Molecular Genetics, and Head of the Harvard Program in Virology at the Department of Microbiology, Blavatnik Institute, at Harvard Medical School. He is scheduled to visit us and present a seminar at UPMC Hillman Cancer Center. Read more about them by clicking here. *(Host: Dr. Shou-Jiang Gao)*

3/22 - Dr. Masa Shuda will present his tenure seminar.

4/5 - Dr. Kathy Shair will present her tenure seminar.

Dr. Erle Robertson - April 12

Dr. Erle Robertson, Harry P. Schenck Professor in Otorhinolaryngology Program Leader, Tumor Virology Training Program, University of Pennsylvania, Department of Microbiology is scheduled to present this spring. Dr. Robertson's lab is geared towards the elucidation of viral induced oncogenesis. The area of their investigation includes basic molecular mechanisms related to understanding the contributory roles on oncogenic human gammaherpesviruses. Read more about them by clicking here. *(Host: Dr. Dr. Patrick Moore)*

Michelle Ozbun, Ph.D. - May 30

Dr. Michelle Ozbun, The Maralyn S. Budke Endowed Professor of Viral Oncology, Cellular and Molecular Oncology Research Program Co-Leader at New Mexico University is scheduled to present a seminar at UPMC Hillman Cancer Center. Read more about them by clicking here. *(Host: Dr. Masa Shuda)*

In Person CVP-WIPs Continue

The CVP-WIP Seminar Series continues in a hybrid format. Pizza is provided for lunch. Location: **The Assembly *Suite B1610*** (Below the Atrium floor). **Zoom Meeting ID: 948 4456 7739, Passcode: 007219.** To join the meeting virtually, click or scan the QR code:

The remaining CVP-WIP schedule is as follows:

3/3: **Saumen Sarkar** - *Faculty*
3/17: **Alan Baeckerholm** - *Shair Lab*
3/31: **Hu Zhang** - *Guo Lab*
4/14: **Lindsey Robinson-McCarthy** - *Chang / Moore Lab*
4/28: **Jenna Nosek** - *DeLuca Lab*
5/12: **James Li Wan** - *Chang / Moore Lab*
5/26: **Ling Ding** - *Gao Lab*
6/9: **Tom Smithgall** - *Faculty*
6/23: **Marwa Ibrahim** - *Guo Lab*

Upcoming CVP-COE Joint Symposium This Fall

Mark your calendar for a symposium on Tuesday, October 10th, 2023 in the Assembly Building.

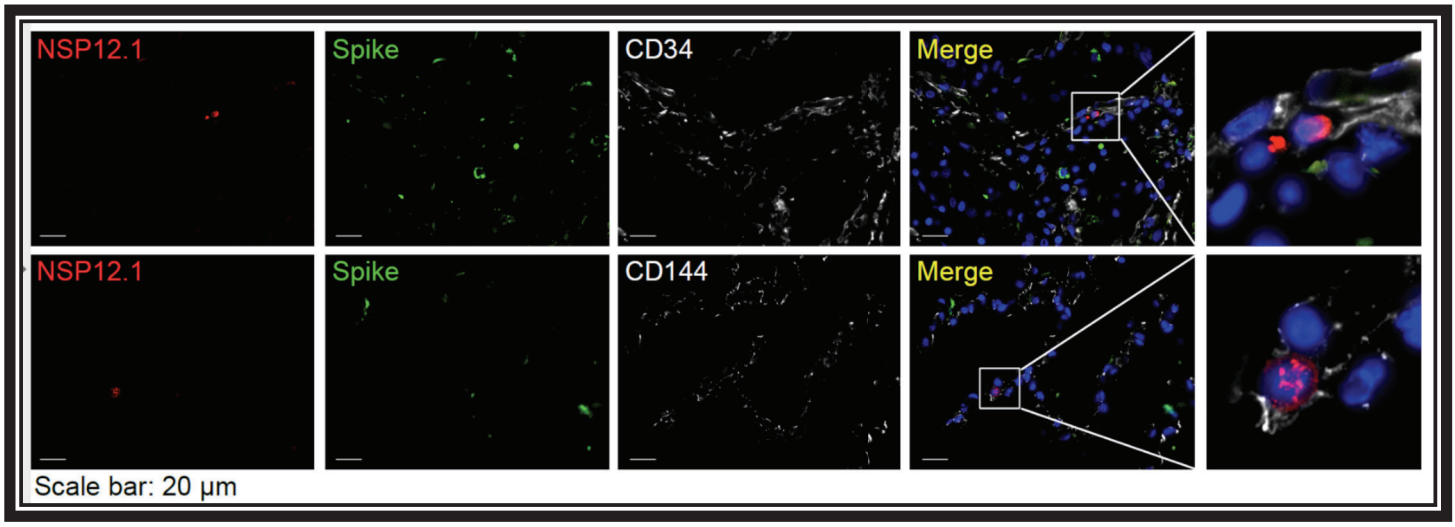
The symposium will featured keynote speaker the *Nobel Laureate* **Dr. Charles Rice** from Rockefeller University. This will be a joint symposium with the Office of Community Outreach and Engagement (COE). Symposium program will be available soon.

Exciting Sciences

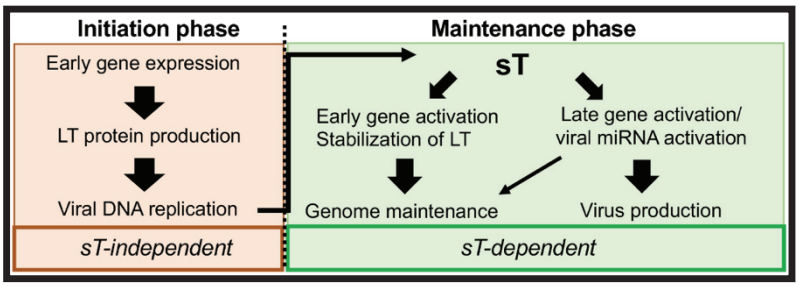
CVP Collaboration Bears Fruit

In collaborative study with multiple groups within the CVP, Siying Guo (Chang-Moore lab) and Wen Meng (Gao lab) published on a rat monoclonal antibody developed to detect the SARS-CoV-2 RNA-dependent RNA polymerase (RdRp) and showed expression of the viral RdRp in lung cells on autopsy cases from persons dying from COVID-19.

Meng W, Guo S, Cao S, Shuda M, Robinson-McCarthy LR, McCarthy KR, Shuda Y, Paniz Mondolfi AE, Bryce C, Grimes Z, Sordillo EM, Cordon-Cardo C, Li P, Zhang H, Perlman S, Guo H, Gao SJ, Chang Y, **Moore PS**. *Development and characterization of a new monoclonal antibody against SARS-CoV-2 NSP12 (RdRp)*. J Med Virol. 2023;95(1):e28246.



Merkel cell polyomavirus small T is an essential viral protein for viral genome maintenance

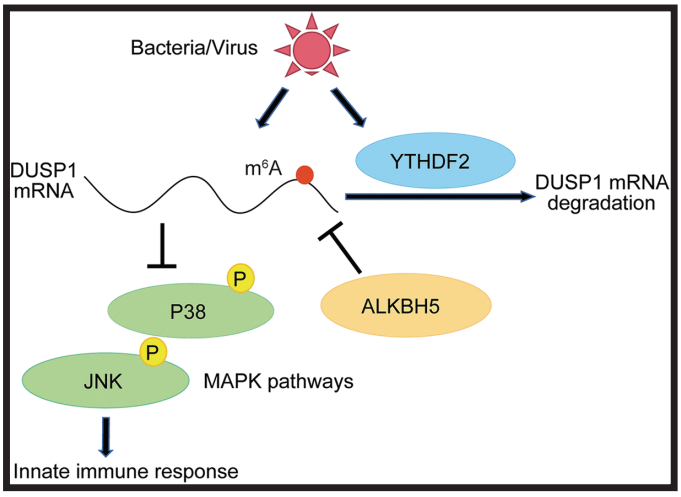


Dr. Masahiro (Masa) Shuda's laboratory is studying Merkel cell polyomavirus (MCV), a causal agent of human Merkel cell carcinoma, and has identified that viral small T antigen (sT) is essential for virus replication and virus production. By exploiting a sT deletion mutant virus MCVΔsT, the Shuda Lab showed that viral gene expression is compromised in MCVΔsT replicating cells. The cellular protein CBP, which promotes gene expression by acetylating histone proteins, was also identified to be a sT protein interactor that mediates sT-induced viral gene activation.

Dr. Shuda, as well as Drs. Patrick Moore and Yuan Chang, previously demonstrated that sT is a major tumor-inducing protein of this virus. The current study further emphasizes the importance of sT as a viral persistence factor that controls virus replication and infectious virus production. This work was recently published in PLoS Pathogens with lead authors Kyle Rapchak and Shiva Yagobian (PLoS Pathog. 2022 Dec 27;18(12) :e1011039)

N6-Methyladenosine and Reader Protein YTHDF2 Enhance the Innate Immune Response

In a collaborative study, Drs. Gao and Huang's groups have revealed that, in response to viral and bacterial infections, dual-specificity phosphatase-1 (DUSP1) transcript and its N6-methyladenosine (m6A) level rapidly increase together with the m6A reader protein YTHDF2, resulting in enhanced YTHDF2-mediated DUSP1 transcript degradation. This leads to increased expression of innate immune response genes including IL1□, CSF3, TGM2 and SRC through activation of p38 and JNK mitogen-activated protein kinases (MAPKs) pathways.

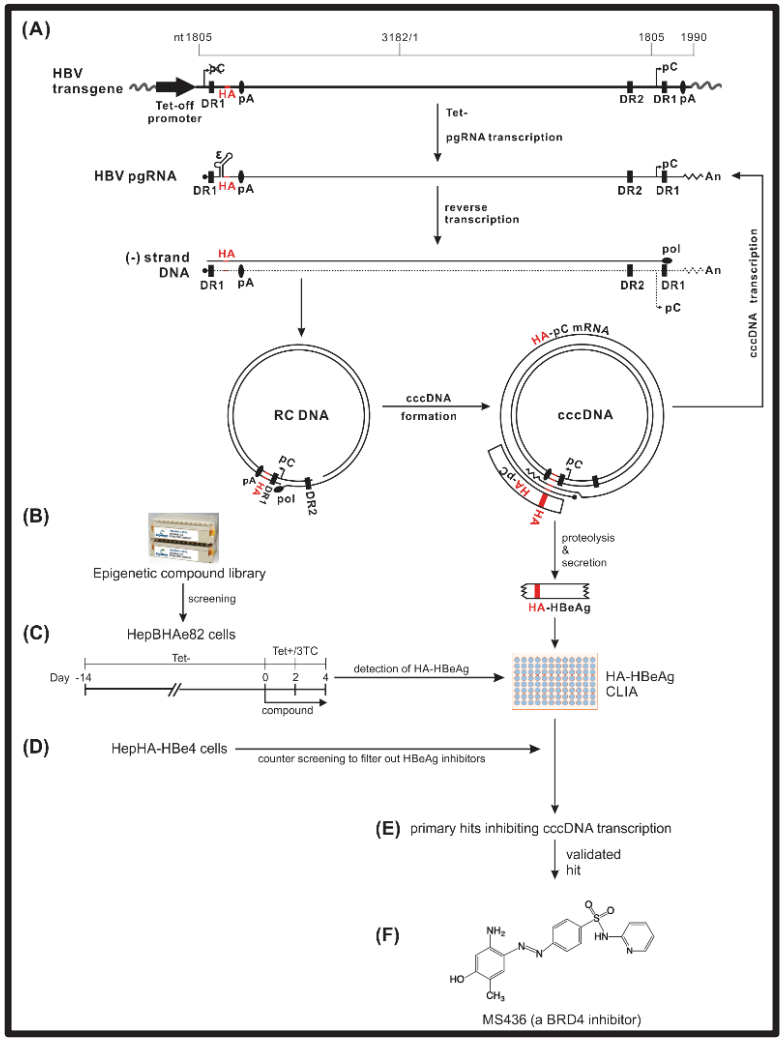


The study demonstrates that m6A and reader protein YTHDF2 orchestrate optimal innate immune response during viral and bacterial infections by downregulating the expression of a negative regulator DUSP1 of the p38 and JNK pathways that are central to innate immune response against pathogenic infections.

Feng J, Meng W, Zhang T, Chen LP, Zhang XQ, Markazi A, Yuan WM, **Huang YF, Gao S-J**. *N6-methyladenosine and reader protein YTHDF2 enhance innate immune response by targeting DUSP1 mRNA degradation and activating mitogen-activated protein kinases during bacterial and viral infections.* mBio, 2023, e0334922. doi: 10.1128/mbio.03349-22. Online ahead of print.

Screening of an epigenetic compound library identifies BRD4 as a potential antiviral target for HBV cccDNA transcription

HBV cccDNA is the persistent form of viral genome, which exists in host cell nucleus as an episomal minichromosome decorated with histone and non-histone proteins. cccDNA is the authentic viral transcript template and resistant to current antivirals. Growing evidence shows that the transcriptional activity of cccDNA minichromosome undergoes epigenetic regulations, suggesting a new perspective for anti-cccDNA drug development through targeting histone modifications. In a paper published in Antiviral Research (IF: 10.10), Dr. Guo's group screened an epigenetic compound library in the cccDNA reporter cell line HepBHAe82, which produces the HA-tagged HBeAg in a cccDNA-dependent manner. Among the obtained hits, a bromodomain-containing protein 4 (BRD4) inhibitor MS436 exhibited marked inhibition of cccDNA transcription in both HBV stable cell line HepAD38 and HepG2-NTCP or primary human hepatocyte infection system under noncytotoxic concentrations. Chromatin immunoprecipitation (ChIP) assay demonstrated that MS436 dramatically reduced the enrichment of H3K27ac, an activating histone modification pattern, on cccDNA minichromosome. RNAseq differential analysis showed that MS436 does not drastically change host transcriptome or induce any known anti-HBV factors/pathways, indicating a direct antiviral effect of MS436 on cccDNA minichromosome. Interestingly, the MS436-mediated inhibition of cccDNA transcription is accompanied by cccDNA destabilization in HBV infection and a recombinant cccDNA system, indicating that BRD4 activity may also play a role in

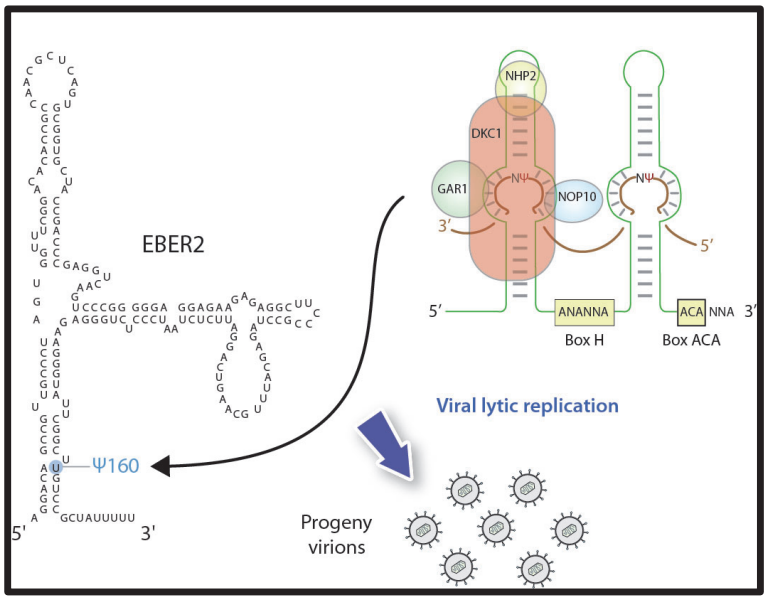


cccDNA maintenance. Furthermore, depletion of BRD4 by siRNA knockdown or PROTAC degrader resulted in cccDNA inhibition in HBV-infected HepG2-NTCP cells, further validating BRD4 as an antiviral target. Taken together, this study has demonstrated the practicality of HepBHAe82-based anti-HBV drug screening system and provided a proof-of-concept for targeting HBV cccDNA with epigenetic compounds.

Yu X, Long Q, Shen S, Liu Z, Chandran J, Zhang J, Ding H, Zhang H, Cai D, Kim ES, Huang Y, **Guo H**. *Screening of an epigenetic compound library identifies BRD4 as a potential antiviral target for hepatitis B virus covalently closed circular DNA transcription.* Antiviral Res. 2023 Feb 1; 211:105552.

RNA Modification of EBV Noncoding RNA Facilitates Viral Replication

Epstein-Barr virus expresses a plethora of noncoding RNAs. Foremost among these in terms of copy number are the EBV-encoded RNA 1 (EBER1) and EBER2. Both transcripts are expressed at approximately a million copies per cell and are thus the most prominent viral factors in host cells.

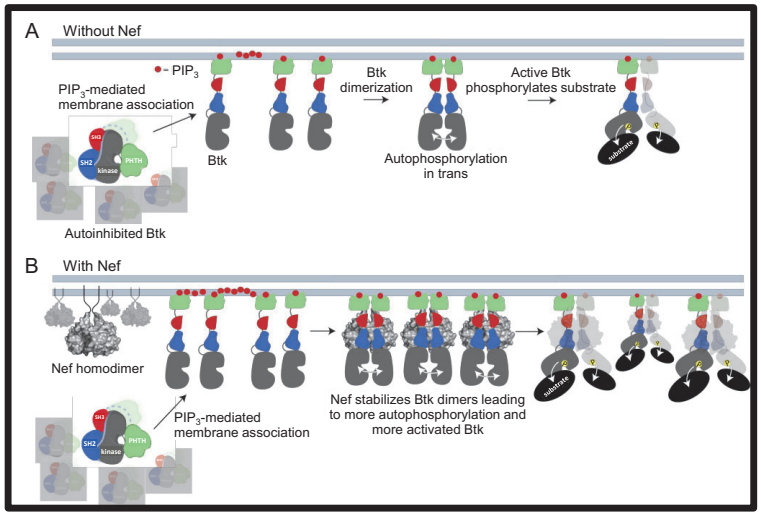


The Lee lab is interested in RNA modifications of EBERs and recently showed that EBER2 is pseudouridylated at a single nucleotide. This was shown using HydraPsiSeq, a recently developed technique entailing next-generation sequencing to map pseudouridylation sites. The writer for this modification was shown to be the snoRNA-dependent enzymatic machinery that relies on base pairing between EBER2 and the host box H/ACA-type SNORA22 to deposit pseudouridine (Ψ) within EBER2. The Lee lab employed a technique developed in their lab called 2CIMPL to identify this interacting RNA-RNA pair. Of physiological relevance, loss of pseudouridylation in EBER2 impairs viral lytic replication of progeny EBV genomes. This study thus provides another example for how RNA modifications contribute significantly to noncoding RNA function.

Henry BA, Marchand V, Schlegel BT, Helm M, Motorin Y, **Lee N**. *Pseudouridylation of Epstein-Barr virus noncoding RNA EBER2 facilitates lytic replication.* RNA. 2022 Nov;28(11):1542-1552. doi: 10.1261/rna.079219.122.

How HIV-1 hijacks Tec-family tyrosine kinases to promote viral replication

Viruses ensure successful replication, in part, by subverting host signaling pathways and HIV-1 is no exception. Using biochemical and cellular assays, Manish Aryal (a Molecular Biophysics and Structural Biology Ph.D. student in the Smithgall lab) uncovered how the Nef protein of HIV-1 activates the Tec-family kinase Btk, which promotes HIV-1 replication in myeloid cells. Nef, which is myristoylated and naturally forms homodimers at the cell membrane, was previously shown to recruit Btk (as well as the CD4 T cell homolog Itk) to form stable complexes with constitutive kinase activity. Tec-family kinase activation by Nef drives viral transcription through the proviral LTR, boosting replication.



Btk and Itk are multidomain protein-tyrosine kinases with essential roles in antigen receptor signal transduction. Both kinases have regulatory PH, SH3, and SH2 domains in addition to the catalytic kinase domain. In the present study, Nef was shown to promote Btk autophosphorylation by stabilizing Btk homodimer formation through a unique mechanism stabilizing protein-protein interaction between the SH3-SH2 regulatory unit. This mechanism is distinct from the physiological activation mechanism, which requires PIP3

generation in the membrane and an intact PH domain, and from the previously reported mechanism of Src-family kinase activation by Nef. Remarkably, this single viral protein has evolved independent mechanisms for activation of two host cell tyrosine kinase families, which points to the importance of these interactions for HIV-1 replication and persistence.

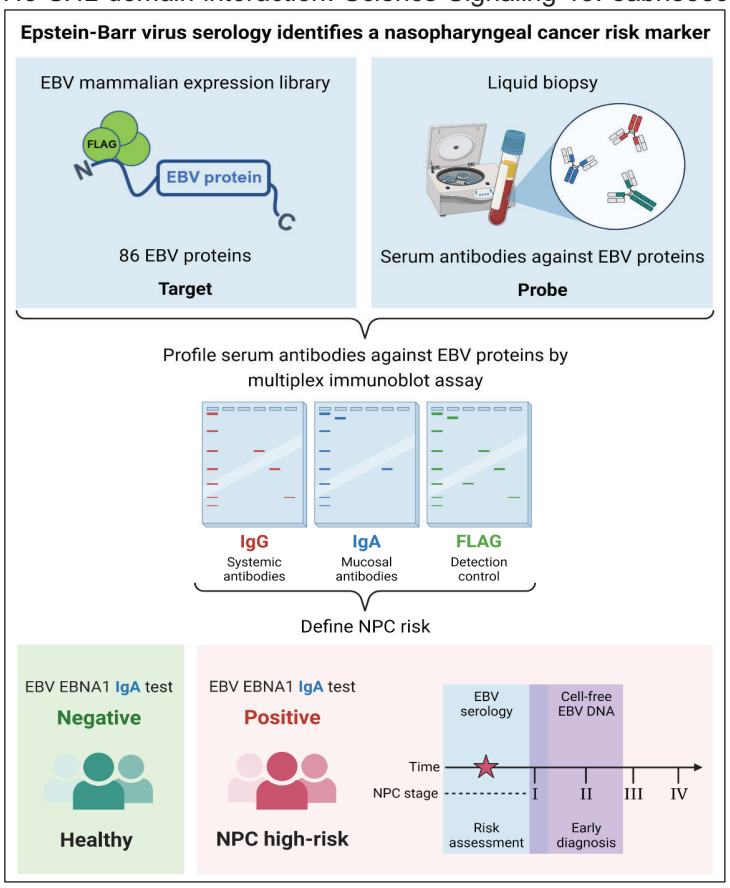
Proposed model of Nef-induced Btk activation. (A) Autoinhibited Btk adopts a closed, cytoplasmic structure with multiple intramolecular interactions between the kinase domain and the regulatory PHTH, SH3, and SH2 domains. In this conformation, the PHTH domain occludes the Btk activation loop (green position) while docking on the N-lobe of kinase domain in crystal structure (light green position). Under physiological conditions, PI3K generates PIP3 (red circles) in the cell membrane which recruits Btk through its PHTH domain leading to homodimer formation, autophosphorylation in trans, kinase activation, and substrate phosphorylation. (B) In HIV or SIV-infected cells, Nef is expressed and targeted to the membrane by virtue of myristoylation where it forms homodimers. Nef also triggers PI3K activation (not shown) to enhance membrane PIP3 levels and Btk recruitment. Nef dimers interact with and stabilize Btk dimers through SH3-SH2 interactions, enhancing kinase autophosphorylation and activity. Nef interaction may also sustain Btk residence on the membrane, thus enhancing signaling to promote viral replication.

Aryal M, Lin D, Regan K, Du S, Shi H, Alvarado JJ, Ilina TV, Andreotti AH, **Smithgall TE.** *The HIV-1 protein Nef activates the Tec family kinase Btk by stabilizing an intermolecular SH3-SH2 domain interaction*. Science Signaling 15: eabn8359, 2022.

Assessing nasopharyngeal carcinoma risk via antibodies against Epstein-Barr virus

Molecular features distinguishing Epstein-Barr virus (EBV) infection in nasopharyngeal carcinoma (NPC) can be exploited as a molecular biomarker for early diagnosis. The challenge is to identify biomarkers to assess the risk of NPC development. Risk assessment has the benefit of identifying high-risk groups for clinical follow-up which can dramatically reduce the healthcare cost of NPC population screens.

The Shair lab recently published a study profiling serum from healthy individuals that later developed NPC in a case-control study with consideration for mammalian-produced proteins derived from an EBV strain that best represents NPC tumors. IgA against EBV nuclear antigen 1 (EBNA1) measured by a multiplex immunoblot assay was shown to be a top biomarker for risk assessment. In a discovery and validation cohort from Singapore and Shanghai, China, sensitivity and specificity values were both 100% for blood drawn up to 4 years before NPC diagnosis. The EBNA1 IgA assay shows promise as a liquid biopsy test for NPC risk prediction in population screens.



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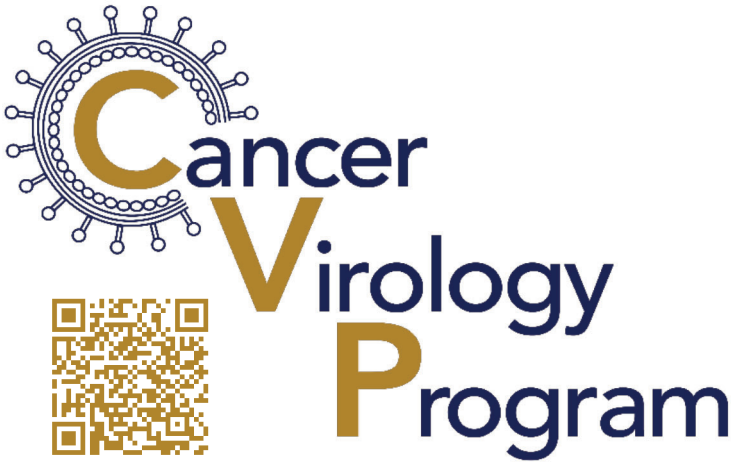
About the Cancer Virology Program (CVP):

Viruses are the cause of approximately 15% of human cancers. CVP is dedicated to research on the viruses causing human cancer as well as using viruses as tools to fight cancer. The study of tumor viruses has led to important discoveries in cancer research, including the identification of numerous oncoproteins and tumor suppressor proteins critical for the development of all cancers.

Learn more about the CVP by scanning or clicking the QR code.



CVP Member List 2023

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