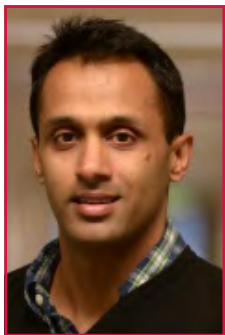


RETRO-ACTIVE NEWS

Newsletter of the Center for Retrovirus Research
at The Ohio State University

2019 Highlights

Dr. Amit Sharma awarded an NIH-R00 to study host innate immune responses as a barrier to cross-species retrovirus transmission



Dr. Amit Sharma, Assistant Professor, Departments of Veterinary Biosciences and Microbial Infection and Immunity and Center member was awarded a **NIH-R00 grant (\$390,151)** to study cross-species retrovirus transmissions.

Macaque model systems are critical gatekeepers for testing HIV-1 prevention methods and for studies of HIV-1 transmission and pathogenesis. HIV-1 does not persistently infect macaques due to restriction by several macaque-specific restriction factors necessitating the use of chimeric SIV/HIV-1 viruses (SHIVs).

During the K99 phase of this grant, in contrast to the adapted SHIVs, it was found that the circulating SHIVs have lower replication kinetics in macaque lymphocytes and are sensitive to type-1 interferon (IFN). The HIV-1 envelope (env) gene was identified as a major determinant of both replication and sensitivity to the

IFN response in macaque lymphocytes. Moreover, it was demonstrated that serial macaque-passage selects for IFN-resistant SHIV variants that have higher replication kinetics and increased Env content. Macaque Interferon-induced Transmembrane Proteins (IFITMs) were also identified as host-factors that limit replication of circulating SHIVs in macaque lymphocytes.

The R00 phase of this grant will continue to characterize the host-viral interactions that selectively restrict replication of circulating SHIVs. During the R00 phase: 1) characterization of the viral determinants in env of the serial macaque-passaged SHIVs will be performed; 2) a novel example of cross-species host-viral interaction will be explored by characterizing the post-transcriptional regulation of HIV-1 envelope gene-expression in macaque lymphocytes; and 3) the mechanism of SHIV restriction by macaque IFITMs will be elucidated. Upon completion, this research proposal will help understand how macaque-specific IFN responses restrict circulating SHIVs.

Dr. Patrick Green honored by the International Retrovirology Association



Dr. Patrick Green was the 2019 recipient of the Dale McFarlin Award. This is the highest honor, awarded every two years by the International Retrovirology Association, for outstanding impact and service to the international retrovirology community.

The award was presented at the 19th International Conference on Human Retrovirology (April 24-26, 2019) in Lima, Peru.

Dr. Amanda Panfil, PhD joins the Ohio State faculty and Center for Retrovirus Research



Dr. Amanda Panfil was recruited to join the Department of Veterinary Biosciences and the Center for Retrovirus Research and Ohio State Comprehensive Cancer Center.

Dr. Panfil received her doctoral training with Dr. Shannon Kenney at the University of Wisconsin-Madison working on cellular regulation of

Epstein-Barr virus lytic reactivation. She then completed her postdoctoral training with Dr. Patrick Green at The Ohio State University studying the molecular pathogenesis of human T-cell leukemia virus type 1 (HTLV-1).

During her postdoc, Dr. Panfil focused on both viral and cellular factors that regulate T-cell transformation and induction of leukemia/lymphoma by HTLV-1. She found the epigenetic factor protein arginine methyltransferase 5 (PRMT5) is upregulated in HTLV-1-mediated transformation and selective inhibition using novel small molecule inhibitors alters viral gene expression

and HTLV-1-infected cell survival. This work has been a necessary first step to show PRMT5 does represent a viable target and potential strategy to treat patients with HTLV-1-associated diseases.

Her research also utilized comparative studies between the anti-sense proteins HBZ (HTLV-1; pathogenic) and APH-2 (HTLV-2; non-pathogenic). These studies have provided important information about the biological properties of these anti-sense proteins in the viral life cycle and has also provided key clues to the pathogenesis of HTLV-1.

Dr. Panfil's recent work with HTLV comparative studies has currently led her to study the importance of Env-1 after infection and its contribution to transformation tropism and pathogenesis. As she begins her independent program here at Ohio State, her laboratory will continue to work with HTLV comparative studies and study genetic and epigenetic regulation of HTLV-1 gene expression and oncogenesis.

Welcome Amanda!

Dr. Shan-Lu Liu's new publication in PNAS uncovers new facets of HIV-host interactions



A new study led by **Dr. Shan-Lu Liu** (Professor and Center Member) published in the journal Proceedings of the National Academy of Sciences USA reveals details about the evolutionary contest between HIV Nef and the human immune system that could one day improve treatment.

The group identified new modulators of HIV, which is notoriously 'smart' and well-equipped at evolving to fight its adversaries in the human body. By examining the cellular-level activity in the laboratory, the research team showed that the protein Nef antagonizes another protein called TIM (T cell immunoglobulin and mucin domain), effectively reducing its power to protect human cells and making it easier for the HIV virus to thrive. Nef changes the rules so that the TIM protein is no longer working as well – it lowers its presence on the cell surface, and prevents it from getting out of the cell. Thus, Nef promotes the release of the virus by antagonizing TIM.

This study shows that Nef can counteract the activity of the TIM proteins by increasing their removal from the cell surface and trapping them within the cell. There is also a fascinating interplay between the TIM family of proteins and another group of antiviral factors known as the SERINC proteins.

The ultimate goal of this line of research is to create some sort of "super restriction factor," that would anticipate the evolution of the virus and adequately fight it. This interdisciplinary study was performed in collaboration with Minghua Li, Jingyou Yu, Cong Zeng and Yi-Min Zheng at Ohio State, Abdul Waheed and Eric Freed at NIH/NCI, Amin Feizpour, Bjoern Reinhard and Suryaram Gummuru at Boston University, and Hui-Yu Chen and Steven Lin at Academia Sinica. The work is funded by the US National Institutes of Health.

Read More: news.osu.edu/researchers-uncover-new-facets-of-hivs-arms-race-with-human-defense-system/

Dr. Matthew Sullivan, Sanggu Kim and Colleagues awarded a DOE Grant to assess how viruses impact soil microbes



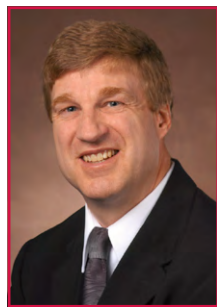
Dr. Sanggu Kim, Assistant Professor in the Department of Veterinary Biosciences and Center member, as part of a multi-disciplinary team received a three year \$3M grant from the Department of Energy entitled “Virus in soils: Key modulators of microbiomes and nutrient cycling”.

In addition to Dr. Kim, the team includes Matthew Sullivan (principal investigator, Professor Ohio State Microbiology and Civil, Environmental and Geodetic Engineering and co-director of IDI’s Microbial Communities Program), and six co-investigators from U Arizona, U Exeter, Laval University, Case Western University, Ashland University and the DOE Berkeley Labs. The project is part of a \$64M initiative

by the Office of Biological and Environmental Research within the Department’s Office of Science.

The Specific Aims of this project are to: 1). Establish ecological paradigms for how dsDNA viruses alter soil microbiomes and nutrient cycles; 2). Develop foundational (eco) systems biology approaches for soil viruses, and; 3). Develop critically needed model systems, in silico resources, and training for soil viral ecology Together these efforts will establish foundational ecological understanding for the soil microbiome, while also developing key tools and resources needed for transformative advances in soil viral ecology to ultimately address the “development and application of –omics approaches to investigate microbial community processes involved in biogeochemical nutrient cycling in terrestrial ecosystems.”

Dr. Patrick Green awarded NIH R13 meeting grant to help support 31st Workshop on Retroviral Pathogenesis



The International Workshop on Retroviral Pathogenesis has long served as a forum for the exchange of new research findings and concepts on all aspects of retroviral pathogenesis, particularly oncogenesis and immunodeficiencies, on topics ranging from molecular mechanisms to the immunological

parameters of host-virus interaction.

The size and format of the conference, generally between 80 – 100 attendees, supports concentrated interaction and deep engagement over four days.

Pathogens of humans and animals in all retroviral genera are the subject of scientific presentation and vibrant discussion.

The conference has long fostered the professional development of junior investigators by affording them the opportunity to present their current work to a panel of engaged colleagues, many of whom will be assessing their work through peer review, and to serve as Session Chairs.

The 31st Workshop was held October 13-16, 2019 at the University of Padova, Italy. The 32nd Workshop is scheduled for October 7-11, 2020 in Vail Colorado, USA.

Drs. Patrick Green and Kristine Yoder received an NIH R21 to study Genome editing to prevent HTLV-1 disease



Center Members, **Dr. Patrick Green** (Biosciences; College of Veterinary Medicine) and **Dr. Kristine Yoder** (Cancer Biology and Genetics; College of Medicine) were awarded an NIH R21 grant entitled “Genome editing to prevent HTLV-1 disease. We propose a novel approach

utilizing the CRISPR bacterial immunity system to disable the HTLV-1 proviral genome and its tumorigenic effect on T cells.

The CRISPR system includes the Cas9 endonuclease that is targeted by a guide RNA (gRNA) to introduce a

specific double strand break (DSB) into genomic DNA which are largely repaired by the error-prone non-homologous end-joining (NHEJ) pathway in most human cells. Typically repair introduces insertions and deletions (indels) at the junction. The broad effects of using the CRISPR system to target the HTLV-1 genome are unknown.

Ultimately, this exploratory grant will provide a quantitative and adaptable platform for probing the efficiency of CRISPR editing to disable HTLV-1 and prevent or disrupt oncogenesis. These data will yield significant insights into the suitability and practicality of genome editing technologies targeting HTLV-1.



Dr. Shan-Lu Liu Co-organized the First Midwest Virology Symposium at Ohio State

Approximately 250 virologists from more than 30 institutions across the Midwest converged on The Ohio State University campus (October 11-13) for the 1st Midwest Virology Symposium 2019. The three-day inaugural meeting was organized by the Center member and Ohio State's Infectious Diseases Institute - Viruses and Emerging Pathogens (VEP) Program Co-Directors Drs. **Shan-Lu Liu** along with Jacob Yount. Attendees included more than 80 faculty members, as well as postdocs, graduate students, staff scientists, and undergraduate students.

The Keynote address was delivered by Dr. Terence Dermody, Physician in Chief, Scientific Director, Vira I. Heinz Professor and Chair of the Department of Pediatrics of University of Pittsburgh Children's Hospital.

He spoke on "The Amazing Assembly Mechanism of a Viral Nanomachine". Nineteen distinguished virology faculty from the Midwest area, five of them from the Ohio State, were also invited to speak at the meeting.

The meeting received a total of 134 abstracts, 43 of which were selected for short or flash talks. The meeting was co-sponsored by IDI, The Office of Research in Provost's office, the College of Medicine, The Center for Retrovirus Research, the Department of Veterinary Biosciences, the Department of Microbial Infection and Immunity, the Department of Microbiology, as well as the Nationwide Children's Hospital Center for Vaccines and Immunity. The journal "Viruses" sponsored the meeting's Keynote address.

Congratulations!



Professor Li Wu departed Ohio State in October, 2019 to become Chair and Executive Officer of the Department of Microbiology and Immunology at the College of Medicine at University of Iowa. Congratulations Li and we wish you the best in your new position.

The Center for Retrovirus Research 2019 Distinguished Research Career Award

Dr. Masao Matsuoka, MD, PhD, was selected by the Center for Retrovirus Research of The Ohio State University to receive the 2019 Distinguished Research Career Award in recognition of his substantial body of work on human T-cell leukemia virus type 1 (HTLV-1) molecular pathogenesis and adult T cell leukemia (ATL) patient therapies.

Dr. Matsuoka is a physician/scientist and oncologist who received his medical and doctorate degrees from Kumamoto University School of Medicine in Japan. He then completed a postdoctoral fellowship at the University of California, Berkeley. Following his postdoc, Dr. Matsuoka returned to Japan where he became Professor and eventually Director of the Institute for Virus Research at Kyoto University. He currently serves as Professor in the Department of Hematology, Rheumatology and Infectious Diseases at Kumamoto University.

Dr. Matsuoka is a leader and innovator in HTLV-1 research. HTLV-1 was the first identified pathogenic human retrovirus and is the etiologic infectious agent of ATL. Dr. Matsuoka's earlier work uncovered both genetic and epigenetic inactivation of the viral Tax oncogene in ATL cells. These results led to our understanding of how HTLV-1 latency is achieved. He also found that the 3' LTR of the HTLV-1 provirus is remarkably hypomethylated, leading him to the discovery of the anti-sense viral transcript, Hbz. Not only is Hbz expressed in all ATL cells, but Dr. Matsuoka made the pivotal discovery that both the Hbz protein and RNA have proliferative effects in infected T cells. In addition, he found Hbz expressing transgenic mice develop T cell lymphomas – further highlighting the critical role of Hbz along with the transactivator, Tax, in ATL development.

Dr. Matsuoka and his research team are currently focused on the molecular pathogenesis of ATL. As a researcher



Dr. Matsuoka (right) receives Career Award crystal from Center for Retrovirus Research member, Dr. Amanda Panfil (center), and Director, Patrick Green (left). Dr. Matsuoka's distinguished award lecture was entitled "How HTLV-1 causes diseases".

who connects clinical science and retrovirology, his work also involves the establishment of novel therapeutics, such as antivirals and immunotherapy, to ATL and other HTLV-1-associated diseases.

Dr. Matsuoka has published over 200 research articles, reviews and book chapters in the field of retrovirology. He is the associate editor of *Cancer Science* and an editorial board member of *Retrovirology*, *Current Opinion in Virology*, and *Cancer Research*. He was previously awarded the 2011 Retrovirology Prize, which recognizes the achievements of an outstanding retrovirologist.

Dr. Matsuoka's visit was sponsored by the Center for Retrovirus Research, Department of Veterinary Biosciences, Infectious Diseases Discovery Theme, Infectious Disease Institute, and the Comprehensive Cancer Center.

Selected Grants and Recognitions

Matthew Sullivan and Sanggu Kim

DOE, DE-SC0020173 “Viruses in soils: Key modulators of microbiomes and nutrient cycling” (2019-2022)

Patrick Green

NIH, R13CA246140, “31st International Workshop on Retroviral Pathogenesis” (2019)

Patrick Green and Kristine Yoder

NIH, R21AI142794 “Genome editing to prevent HTLV-1 disease” (2019-2021)

Namal Liyanage

NCH CF Pilot Grant NCH, “T cell dysfunction in CF patients with nontuberculous mycobacteria infection” (2019-2021)

Amit Sharma

NIH R00AI125136, “Host innate immune response as a barrier to cross-species retrovirus transmission” (2019-2021)

Amit Sharma

Keynote Talk, Falkenthal Graduate Research Colloquium, Department of Molecular Genetics, The Ohio State University

Student, Post-doc, Research Scientist and Visiting Scholar Awards and Positions

Sarah Golconda, (PhD student; Kim Lab). Recipient of the David White fellowship (2019-2020).

Nancy Tian, (Medical Student; Liyanage Lab). Recipient of the Medical Student Research Scholarship Program award (2019).

Laura Baltierra-Jasso PhD (Postdoctoral Researcher; Yoder Lab). Recipient of Ohio State CCC Pelotonia Postdoctoral Fellowship (2019-2021).

Victoria Maksimova (PhD student; Panfil Lab). Recipient of the C. Glenn Barber Fellowship (2019-2021).

Michael Martinez, DVM (Resident PhD student; Green Lab). Recipient of the Society of Toxicologic Pathology (STP) Student Travel Award to attend and present his research at the STP 38th Annual Symposium (June 22–27, 2019, Raleigh, NC).

Amanda Panfil, PhD (Research Scientist: Green Lab). Recipient of outstanding Poster Award at the International Symposium on Human Retrovirology: HTLV and related diseases (April 23-26, 2019 Lima, Peru).

Michael Martinez, DVM (Resident PhD student; Green Lab). Recipient of The Ohio State University Comprehensive Cancer Center Annual Scientific Meeting poster award (May 8, 2019).

Weili Kong, PhD (Post doctoral Researcher, Zhu Lab) took a Senior Post Doctoral position with Warner Greene, MD, PhD at UCSF Gladstone Institutes to continue his training.

2019 Graduates and Passage of Candidacy Exam

Alice Baek (Kim Lab) successfully passed PhD candidacy exam.

Chathuri Pathirage (Musier-Forsyth Lab) successfully passed PhD candidacy exam

Selected Upcoming Meetings

Symposium on HIV/AIDS

March 5-7, 2020, Palm Springs, CA

Cold Spring Harbor Laboratory “Retroviruses”

May 18-23, 2020, Cold Spring Harbor, NY

American Society for Virology

June 13-24, 2020, Fort Collins, CO

32nd Workshop on Retroviral Pathogenesis

October 7-11, 2020, Vail, CO

Selected Publications

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- Dirajlal-Fargo S, Mussi-Pinhata MM, Weinberg A, Yu Q, Cohen R, Harris DR, Bowman E, Gabriel J, Kulkarni M, **Funderburg N**, Chakhtoura N, McComsey GA. HIV-exposed-uninfected infants have increased inflammation and monocyte activation. *AIDS.* 2019 Apr 1;33(5):845-853. doi: 10.1097/QAD.0000000000002128.
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- Hayes D Jr, Harhay MO, Nicol KK, **Liyanage NPM**, Keller BC, Robinson RT. Lung T-Cell Profile Alterations are Associated with Bronchiolitis Obliterans Syndrome in Cystic Fibrosis Lung Transplant Recipients. *Lung.* 2019 Dec 5;doi: 10.1007/s00408-019-00298-1
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