

RETRO-ACTIVE NEWS

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

2023 Highlights

Amit Sharma is awarded \$5.86M NIH R01 and U54 Duke Center HIV Structural Biology grants to investigate determinants of retroviral replication in non-native hosts for modeling HIV infection



Amit Sharma, PhD, Assistant Professor in Veterinary Biosciences, was recently awarded a \$4,105,608 R01 grant from NIH NIAID for a project entitled, “**Determinants of retroviral replication in non-native hosts for modeling HIV infection**”.

HIV does not replicate in macaques, and thus chimeric simian-human immunodeficiency viruses (SHIVs) are used as surrogates to study HIV infection in macaques. However, most SHIVs fail to replicate in macaques unless they are extensively adapted via serial macaque passage, which is an expensive and labor-intensive process.

The objectives of this research are to: 1) characterize the adaptive changes in Env of serial passaged SHIVs that increase replication and interferon (IFN) resistance; 2) determine the role of N-linked Envelope (Env) glycans in SHIV infection of primary macaque immune cell subsets *ex vivo*, and mucosal transmission and pathogenicity of SHIVs *in vivo*; and 3) evaluate the contribution of five macaque interferon-

induced transmembrane protein homologs, which are upregulated by IFN, in restriction of unpassaged, IFN-sensitive SHIVs. Upon completion, this study will provide mechanistic insights at the host-viral interface that drive selection, adaptation, and pathogenicity of SHIVs in macaques.

In addition to NIH R01, Dr Sharma was also awarded a \$174,551 Collaborative Development Award from the NIAID U54 Duke Center for HIV Structural Biology for a project entitled, “**Defining engineered changes in HIV-1 Envelope that overcome macaque transmission barriers**”.

The objectives of this research are to: 1) investigate the functional basis for higher replication of SHIVs encoding point mutations in the gp41 transmembrane fusion subunit of Env; and 2) study the structural changes in Env induced by point mutations in the gp41 subunit of Env. Upon completion, this study will provide fundamental understanding of how modulation of Env conformational dynamics through engineered mutations can help overcome macaque transmission barriers.

NIH/NCI Diversity Supplement Awarded to Drs. Amanda Panfil and Patrick Green



Dr. Amanda Panfil, Assistant Professor in Veterinary Biosciences and Center member and **Dr. Patrick Green**, Professor and Director of the Center for Retrovirus Research, were awarded a 2-year \$155,717 supplement from the NIH’s Research Supplements to Promote Diversity in

Health-Related Research Program. The award, funded by the National Cancer Institute, will be used to support Rocio Zaldivar, a PhD Graduate Research Associate in the Molecular, Cellular and Developmental Biology graduate program. She will work on Project 1 of the Parent P01 Program Project Grant, “*Retrovirus Models of Cancer*”. Dr. Panfil will serve as the lead mentor.

Shan-Lu Liu is awarded \$1.5 M USDA contractual grant to study zoonotic transmission of SARS-CoV-2



Dr. Shan-Lu Liu, Associate Director of the Center and Co-director of the Viruses and Emerging Pathogens Program of The Ohio State University's Infectious Diseases Institute was awarded an USDA contractual grant, titled "**Understanding the molecular mechanisms of zoonotic transmission of SARS-CoV-2**".

SARS-CoV-2 continues to evolve and affect the lives of millions and presents a constant challenge to human and animal health. The transmission and propagation of the virus through an animal host can lead to the rapid accumulation of novel mutations with unknown consequences in animals and humans. This study seeks to better characterize the potential for zoonotic transmission of SARS-CoV-2 and to understand how virus mutations acquired in animal hosts can impact animal and human health.

Dr. Liu will test the overarching hypothesis that the evolution of SARS-CoV-2 through an animal host can lead to variants with altered ability to infect humans and other animal species. Specifically, his lab will examine how mutations acquired in animal can increase viral entry into human cells through increasing binding to the viral receptor.

He will also examine how the SARS-CoV-2 spike protein on the surface of viral particle evolves under the selection pressure of animal ACE2 and impacts on viral entry into human airway cells. In addition, Dr. Liu will investigate how animal isolates of SARS-CoV-2 and *in vitro* selected viruses can be resistant to human and animal sera, resulting in transmission of them into human and animal populations. Together, results from this grant will enhance our understanding of the impacts of SARS-CoV-2 spread in humans and animals, hence allowing for improved control efforts in vaccination development, COVID-19 treatment and animal surveillance.

NIH-National Institutes of Allergy and Infectious Diseases grant awarded to Dr. Cody Warren to identify genetic barriers to animal virus replication in human cells



Dr. Cody Warren, Assistant Professor, Department of Veterinary Biosciences and Center member, was awarded an NIH-R00 grant (\$249,000) to develop and demonstrate an experimental pipeline that will distinguish between animal viruses facing few blocks to replication in human cells

from those with many.

Host genetics plays a critical role in the species specificity of viruses. Divergence in host proteins used for virus entry (cellular receptors), replication (cellular cofactors), and antiviral immunity (restriction factors) can serve as potent barriers to virus infection in a new host species. Using hypothesis-driven studies and high throughput genomic approaches, he will systematically characterize this host-virus interaction landscape for an understudied family of primate viruses (simarteriviruses).

Aim 1 will assess the compatibility of diverse simarteriviruses with the human version of their cellular receptor, CD163. It will also assess the ability of these viruses to replicate in human CD163 expressing human cells. Aim 2 will follow up on hits from a recently completed CRISPR screen that identified essential cofactors required for viral replication. They will use evolutionary signatures of positive natural selection to identify host proteins that are likely to engage simarteriviruses in a species-specific manner. Aim 3 will follow up on hits from a recently completed cDNA screen to identify novel antiviral factors. Using a series of gene knockdowns and complementations, they will evaluate the genetic barriers to simarterivirus replication in human cells (Aims 1-3).

Taken together, these aims will establish an experimental framework to evaluate the zoonotic risk of an understudied family of animal viruses.

Kristine Yoder is awarded \$1.9M and \$2.3M NIH R01 awards to study retroviral integration complexes



Kristine Yoder, PhD, Associate Professor in Cancer Biology and Genetics in the College of Medicine, has been awarded two NIH R01s titled “Determinants of Architecture on Retroviral Intasome Mechanics” and “HIV-1 Intasome Assembly and Function”.

The Yoder lab is focused on unraveling the mysteries of retroviral integration complexes, also known as intasomes. Retroviral intasomes are comprised of varying multimers of integrase. For example, prototype foamy virus (PFV) intasomes are a tetramer of integrase bound to the viral cDNA ends while HIV-1 intasomes appear to be a dodecamer of integrase.

The underlying reasons for the evolution of diverse multimers remain a mystery, as does their potential impact on pathogenesis and interactions with host chromatin. Dr. Yoder and her team aim to address these gaps through innovative approaches, employing single molecule imaging and biochemical assays. Their research will delve into the intricacies of intasome assembly progressions, investigating how different multimeric forms dynamically interact with defined target DNA and chromatin substrates both *in vitro* and *in cellulo*. This ground-breaking work not only expands our understanding of retroviral biology but also holds promise for advancements in therapeutic interventions.

Dr. Patrick Green is awarded an NIH R13 meeting grant to help support 33rd International Workshop on Retroviral Pathogenesis



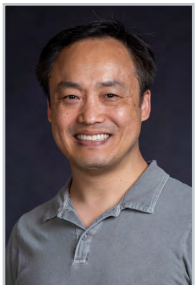
The International Workshop on Retroviral Pathogenesis has long served as a forum for the exchange of new research findings and concepts on all aspects of retroviral pathogenesis, particularly oncogenesis and immunodeficiencies, on topics ranging from molecular mechanisms to the immunological parameters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

virus interaction. The size and format of the conference, generally between 75 – 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 33rd Workshop was held December 4-8, 2023 in Trento, Italy (local host: Massimo Pizzato - University of Trento).

Department of Defense (DOD) grant awarded to Dr. Sanggu Kim to improve T-cell lymphoma therapy



Dr. Sanggu Kim, Associate Professor in Veterinary Biosciences and Center member, was awarded a 3-year DOD grant (\$567,000) entitled “Targeted antibody and immunotoxin combination improve T-cell lymphoma therapy.” The working hypotheses are that (i) follicular T cells are spared in CD3-IT treatment owing to the

protective effect of the anatomic structure of lymphoid B-cell follicles and that (ii) pretreatment with a CD40L blocker prior to CD3-IT treatment will enhance T-cell depletion.

CD40L blockade has been shown to effectively dissociate the B-cell follicles. It is anticipated that CD40L-mAb and CD3-IT co-treatment will enhance T-cell depletion and thereby increase response rates, reduce treatment resistance, and decrease disease relapse after CD3-IT treatment. Engineered toxins will further improve the efficacy and safety of CD3-IT by preventing toxin-mediated vascular leakage syndrome (VLS).

The goal is to identify the mechanisms underlying follicular T-cell resistance in CD3-IT treatment and to develop innovative therapeutic strategies to overcome such treatment resistance and thereby improve T-cell lymphoma therapy.

The Center for Retrovirus Research 2023 Distinguished Research Career Award

Dr. Wesley I. Sundquist was selected by the Center for Retrovirus Research of The Ohio State University to receive the 2023 Distinguished Research Career Award in recognition of his seminal contributions to the field of molecular and structural biology of retroviruses, particularly HIV.

Dr. Wesley Sundquist is the Samuels Professor and Chair of Biochemistry at the University of Utah School of Medicine. He graduated from Carleton College, Northfield, Minnesota with a degree in Chemistry and from Massachusetts Institute of Technology with a PhD in chemistry, mentored by Dr. Steve Lippard. Dr. Sundquist then did his postdoctoral training at the MRC Laboratory of Molecular Biology, in Cambridge, England with Dr. Aaron Klug, before joining the faculty in the Department of Biochemistry at the University of Utah in 1992.

Dr. Sundquist has made many significant contributions to the field of molecular and structural biology of retroviruses, in particularly HIV. He used integrated approaches by combining structural and functional analysis to develop the fullerene cone model of the HIV-1 capsid, which explains intrinsic architectural principles of retroviruses. He was the first to report the crystal structure of the HIV MA protein as well as the 3D structure of the N-terminal domain of the HIV-1 CA protein (1996). He then demonstrated HIV-1 capsids belong to a family of geometric objects comprising extended hexagonal lattices and 12 pentagons, called fullerene cones (1999).

In 2001, Dr. Sundquist discovered that HIV-1 budding is achieved by recruitment of the ESCRT pathway, and then identified components of this pathway in humans, and determined structures and mechanisms of pathway proteins. Recently, Dr. Sundquist has applied emerging paradigms for enveloped virus assembly to the design and characterization of new proteins that can assemble into nanocages, bud from mammalian cells, and carry cargoes into new target cells. In 2020, he described the reconstitution of HIV-1 reverse transcription initiation, double-strand DNA synthesis, and target integration of the HIV-1 genome in a cell free system, starting with purified viral capsids.



Dr. Wesley I. Sundquist holds the 2023 Distinguished Career Award crystal.

Dr. Sundquist's research continues to focus on understanding the architecture and assembly of retroviral particles, the mechanisms of intrinsic host cell defenses, and the process of virus budding using state-of-the-art approaches including NMR, EM and crystallographic studies.

Dr. Sundquist has published numerous papers in leading scientific journals including Cell, Nature, PNAS, and Science. He is an editor or on the editorial board of many journals, including eLife. Over the years, he has received many awards, including Searle Scholars Award, the ASBMB Amgen Award for the Application of Biochemistry and Molecular Biology to the Understanding of Disease, the Bernard Fields Award for Retrovirology, and a Distinguished Alumnus Award from Carleton College. He was elected to the American Academy of Arts and Sciences in 2011 and the National Academy of Science in 2014. Dr. Sundquist was also named as University Distinguished Professor, and won the prestigious Rosenblatt Award for Excellence from the University of Utah in 2017.

As an effective mentor, Sundquist has trained more than 40 graduate students and postdocs, many of whom currently hold independent positions in academic and private-sector institutions.

Dr. Sundquist's distinguished award lecture was entitled "Structure and function of the HIV capsid." His visit was sponsored by the Center for Retrovirus Research, Department of Veterinary Biosciences, Infectious Disease Institute, and the Comprehensive Cancer Center.

PhD Graduate Student Highlight



John (Jack) P. Evans, a Molecular, Cellular and Developmental Biology Program student of The Ohio State University in **Dr. Shan-Lu Liu's lab** at the center defended his PhD dissertation in March 2023.

Jack's thesis work was focused on the impact of SARS-CoV-2 evolution and variants of concern on neutralizing antibody responses induced by COVID-19 mRNA vaccine and/or natural infection. His work has provided critical insights into the

mechanisms of SARS-CoV-2 immune evasion and immune imprinting with regards to COVID-19 vaccine development.

During his PhD training (2018-2023), Jack has published **25 papers**, including **18 first or co-first author papers**. He was also a recipient of *Ohio State's Distinguished Graduate Student Fellowship* from the Graduate School, a recipient of the *C. Glenn Barber Fund Fellowship* from the College of Veterinary Medicine. After graduation, Jack took a Scientist position at *GSK, Viral Vaccines R&D*. Congratulations!

Selected Grants and Recognitions

NIH R13CA287389-01 (**Patrick Green**) 33rd International Workshop on Retroviral Pathogenesis (2023)

NIH R00 AI151256 (**Cody Warren**) Identifying genetic barriers to animal virus replication in human cells: Insights into zoonosis (2023-2025)

NIH R21 AI180295 (**Cody Warren / Adam Bailey**) Arterivirus receptors: rules of engagement for cross-species infection (2023-2025)

NIH L70 AI178789 (**Cody Warren**) Control of influenza A virus replication in macrophages: a window into viral pathogenesis (2023-2025)

Ohio State IDI Interdisciplinary Research Seed Grant (**Cody Warren / Andy Bowman / Mark Peeples**) An experimental pipeline to evaluate zoonotic risk: a strategy for influenza virus pandemic prevention (2023-2024)

R01AI150496-06 (**Kristine Yoder**) HIV intasome assembly and function (2023-2028)

R01GM150003-01 (**Kristine Yoder / Richard Fishel**) The determinants of architecture on retroviral intasome mechanics (2023-2027)

NIH R01MH134402 (**Jian Zhu**, contact PI) Target Host Epigenetic Regulation of HIV Proviruses to Reinforce Viral Deep Latency in Microglia (2023-2028)

NIH R01DA059538 (**Jian Zhu**, contact PI) Investigate Host Gene Isoforms Contributing to HIV Persistence in Cocaine Users (2023-2028)

NIH 1R21AI174874-01 (**Ross Larue**) Histone Modifications Guiding HIV Integration (2023-2024)

Ohio State IDI Research Grant (**Ross Larue/Daniel Adu-Ampratwum**) Development of Small Molecule HIV-1 Capsid-targeting Probes (2023-2024)

DOD Idea Award (**Sanggu Kim**) Targeted Antibody and Immunotoxin Combination Improve T-Cell Lymphoma Therapy (2023-2025)

USDA APHIS (**Shan-Lu Liu**) Understanding the molecular mechanisms of zoonotic transmission of SARS-CoV-2 (2023-2025)

Ohio State Comprehensive Cancer Center Leukemia Research Program (**Panfil**) Development of a human T-cell leukemia virus type 1 mRNA vaccine (2023)

Provisional Patent (**Amit Sharma**, Pui-Kai Li, Enming Xing, Shabber Mohammed); Small Molecule Inhibitors for the Treatment and Prevention of Coronavirus Infection.

R35 GM141880-03S1 (**Karin Musier-Forsyth**) Equipment Supplement for Isothermal Titration Calorimeter (2023-2024)

Shan-Lu Liu was named as Editor of Journal of Virology (2023-2028)

Karin Musier-Forsyth was named as Director of the Center for RNA Biology (2023-2028)

Meeting Announcements

Dr. Shan-Lu Liu is the host of the **43rd American Society for Virology (ASV) Annual Meeting**, Columbus, Ohio, June 24-28, 2024 asv.org/asv2024/

Dr. Amit Sharma and Dr. Zandrea Ambrose (University of Pittsburgh) have been named organizers for the **28th West Coast Retrovirus Meeting**, which will be held in Palm Springs, California in October 3-5, 2024.

21st Biennial International Conference on Human Retrovirology: HTLV and Related Viruses. Imperial College London and Royal College of Physicians, London, UK June 2-5, 2024. htlv2024.org

Graduate Student & Post-doc Awards, Career Moves & Positions

Christina Sanders, Makky Mousa-Makky, and Jared Compaleo joined the **Warren lab**

Christina Sanders (**Cody Warren lab**) was a recipient of the 2023 AAI Travel for Techniques Award

Gabby Lee (**Sanggu Kim lab**) received the C. Glenn Barber Fellowship from the College of Veterinary Medicine

Panke Qu (**Shan-Lu Liu lab**) received the C. Glenn Barber Fellowship from the College of Veterinary Medicine

John. P. Evans (**Shan-Lu Liu lab**) moved to GSK and took a Scientist position

Julia Faraone (**Shan-Lu Liu lab**) was awarded for Poster Presentation at Ohio State College of Veterinary Medicine Research Day

Julia Faraone (**Shan-Lu Liu lab**) was awarded the Second Place Award in MCDB 3 Minute Thesis Competition

Yu-Ci Syu (**Karin Musier-Forsyth lab**) took a postdoctoral position in the lab of Stephen P. Goff at Columbia University

Chathuri Pathirage (**Karin Musier-Forsyth lab**) took a postdoctoral position in the lab of Kristin Koutmou at the University of Michigan

Rocio Zaldivar (**Amanda Panfil lab**) awarded a two-year **Diversity Supplement Award** from NIH NCI for her dissertation research.

Rocio Zalvidar (**Amanda Panfil lab**) awarded a one-year **Cellular, Molecular, and Biochemical Sciences Training Grant** from Ohio State Cellular, Molecular, and Biochemical Sciences Graduate Program for her dissertation research (declined due to NIH Diversity Supplement Award).

Joshua Tu (**Amanda Panfil lab**) received a **Travel Award** for Immunology & Infectious Diseases Category Poster Presentation. College of Veterinary Medicine Research Day.

Kyle Ernzen (**Amanda Panfil lab**) received a one-year **C. Glenn Barber Predoctoral Fellowship** from Ohio State College of Veterinary Medicine for his dissertation research.

Kyle Ernzen (**Amanda Panfil lab**) received **Travel Award** for research presentation at ASV 2023. American Society for Virology.

Susan Smith (**Amanda Panfil lab**) received **Travel Award** for research presentation at ACVP 2023. Ohio State Department of Veterinary Biosciences.

Emily King (**Amanda Panfil lab**) received **Travel Award** for research presentation at ACVP 2023. Ohio State Department of Veterinary Biosciences (Summer 2023).

Victoria Maksimova (**Amanda Panfil lab**) received **Travel Award** for Molecular and Cellular Biology Category Poster Presentation. College of Veterinary Medicine Research Day.

Jaideep Seth (**Amanda Panfil lab**) was awarded a one-year **Pelotonia Undergraduate Fellowship** from Ohio State Comprehensive Cancer Center for his research.

2023 Passage of Candidacy Exam

Emily King (Amanda Panfil lab) successfully passed PhD candidacy

Christina Sanders (Cody Warren lab) successfully passed PhD candidacy

Kaylee Grabarkewitz, Joe Kanlong, Morgan Bauer, Mahfam Shariati (Karin Musier-Forsyth lab) passed PhD candidacy

2023 PhD Graduates

Alice Baek and Shihyoung Kim (Sanggu Kim lab) received their PhD

Chathuri Pathirage (Karin Musier-Forsyth lab) received her PhD

John. P. Evans (Shan-Lu Liu lab) received his PhD

Joshua Tu (Amanda Panfil lab) received his MS

Victoria Maksimova (Amanda Panfil lab) received her PhD

Susan Smith (Amanda Panfil lab) received her PhD

Selected Publications

- Azar J, Evans JP, Sikorski M, Chakravarthy K, McKenney S, Carmody I, Zeng C, Teodorescu R, Song NJ, Hamon J, Bucci D, Velegraki M, Bolyard C, Weller KP, Reisinger S, Bhat SA, Maddocks KJ, Gumina RJ, Vlasova AN, Oltz EM, Saif LJ, Chung D, Woyach JA, Shields PG, **Liu S-L**, Li Z, Rubinstein MP. Selective suppression of de novo SARS-CoV-2 vaccine antibody responses in patients with cancer on B cell-targeted therapy. *JCI Insight*, 2023 8(6):e163434.
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