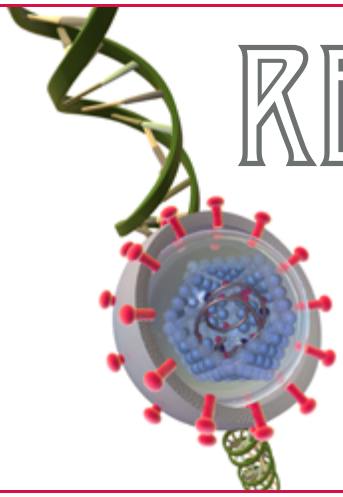


RETRO-ACTIVE NEWS

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

2021 Highlights

Karin Musier-Forsyth and Colleagues Renew Cellular, Molecular and Biochemical Sciences Program (CMBP) T32 Predoctoral Training Grant

Karin Musier-Forsyth (Professor and Ohio Eminent Scholar, Department of Chemistry and Biochemistry), together with co-PI/PD Dr. Jane Jackman (Professor of Chemistry and Biochemistry), renewed an 10-slot predoctoral training grant in Cellular Molecular and Biochemical Sciences (2021-2026). The Cellular Molecular and Biochemical Sciences Program (CMBP) draws faculty and trainees from four related molecular life sciences graduate programs: Microbiology, Molecular Cellular and Developmental Biology, Molecular Genetics, and the Ohio State Biochemistry Program. Four preceptors from the CRR include Drs. Musier-Forsyth, Panfil, Kwiek, and Green.

The goal of the CMBP is to create opportunities for student training not available through other programs on campus by providing: (1) a broader range of rotation choices, (2) interdisciplinary monthly meeting seminars and symposia, (3) coursework that includes an emphasis on the responsible conduct of research, scientific writing, rigor and reproducibility, and training in quantitative skills, (4) career-advancing components including professional development workshops specifically developed for this program, internship opportunities, and Individual Development Plans, and (5) faculty mentor training to ensure a holistic and supportive advisory environment conducive to trainee growth and development.

The unique combination of opportunities offered through the CMBP will continue to increase recruitment and retention of the very best graduate students, in particular from underrepresented minorities and students with disabilities.

Amanda Panfil Funded to Study the Effects of m^{6}A RNA Modifications on the Biology of HTLV-1

Amanda Panfil, Assistant Professor, College of Veterinary Medicine and member of the Center for Retrovirus Research, has been awarded a two-year Ohio Cancer Research Award to study the effects of m^{6}A RNA modifications on the oncogenic retrovirus HTLV-1.

Successful regulation of HTLV-1 gene expression allows the virus to evade immune detection, immortalize infected target cells and establish persistent infection. Consequently, regulation of viral gene expression directly contributes to its pathogenic potential.

This seed grant proposal will test the hypothesis that dynamic m^{6}A modification of HTLV-1 RNA regulates viral gene expression and subsequent viral-mediated cellular proliferation and pathogenesis.

Shan-Lu Liu and Colleagues Discover a New Function of HIV Restriction Factor SERINC in Potentiating the Type I IFN and NF-κB Signaling

Shan-Lu Liu, Professor in the Department of Veterinary Biosciences and Associate Director of the Center for Retrovirus Research published a paper in Science Signaling describing a novel function of HIV restriction factor SERINC in enhancing type I IFN and NF-κB signaling to inhibit infection by HIV and other viruses.

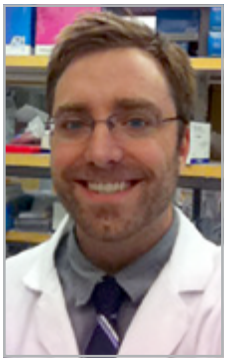
The SERINC (known as "serine incorporator") proteins are the newest HIV host restriction factors that inhibit infection by HIV through their incorporation into virions. In this work, Dr. Liu and colleagues found that SERINC3 and SERINC5 exhibit a new antiviral activity by enhancing the expression of genes encoding type I and NF-κB signaling. SERINC5 was shown to interact with the outer mitochondrial membrane protein MAVS (mitochondrial antiviral signaling) and the E3 ubiquitin ligase and adaptor protein TRAF6, resulting in MAVS aggregation and polyubiquitylation of TRAF6. Knockdown of SERINC5 in target cells increased single-round HIV-1 infectivity, as well as infection by recombinant vesicular stomatitis virus (rVSV) bearing VSV-G or Ebola virus (EBOV) glycoproteins.

Liu and colleagues also examined additional viruses and found that infection by an endemic Asian strain of Zika virus (ZIKV), FSS13025, was also enhanced by SERINC5 knockdown, suggesting that SERINC5 has direct antiviral activities in host cells in addition to the indirect inhibition mediated by its incorporation into virions. Finally, Dr. Liu and colleagues provided evidence that the antiviral activity of SERINC5 is type I IFN–dependent. Together, this work uncovers a previously uncharacterized function of SERINC proteins in promoting NF-κB inflammatory signaling and type I IFN production, thus contributing to its antiviral activities.

Co-authors include Cong Zeng, Tianliang Li, Jingyou Yu, Yi-Min Zheng, Jacob Yount and Haitao Wen at The Ohio State University, and Abdul Waheed and Eric Freed at the NCI HIV Dynamics and Replication Program.

Read more: news.osu.edu/proteins-that-outwit-emerging-and-re-emerging-viruses/

Nicholas Funderburg Receives an NIH R01 to Investigate Cardiovascular Disease Among People Living with HIV



Nicholas Funderburg, Associate Professor, Division of Medical Laboratory Science, School of Health and Rehabilitation Sciences received a four year, $2.8M R01 from the National Heart, Lung, Blood and Sleep Institute (NHLBI) titled " Plaque and Blood Derived Macrophages: A Multi-omic Assessment of Cardiovascular Disease (CVD) Pathogenesis in People Living with HIV (PLWH).

CVD is the leading cause of death among PLWH receiving antiretroviral therapy (ART) and there is ~2-fold greater risk for CVD events in PLWH compared to the risk among HIV- individuals. In this grant, the Funderburg Lab will explore the transcriptional, phenotypic and functional capabilities of monocyte derived macrophages and compare them to the transcriptomic profiles of plaque derived macrophages in PLWH and in HIV negative individuals.

Dr. Funderburg and colleagues hypothesize that ART, directly and indirectly through alteration of the lipidome, contributes to macrophage activation in PLWH and subsequently to increased CVD risk. Previous work from the Funderburg lab has linked activation of monocyte subsets and monocyte derived macrophages to increases in the concentration of multiple lipid classes that may contribute to the development of CVD.

This R01 will also assess the changes in lipid profiles, inflammation and macrophage activation in PLWH receiving statins as lipid lowering therapy. Overall, by exploring the mechanistic relationships among lipids, inflammation and monocyte/macrophage activation, this study may provide insights into the development of atherosclerotic disease in PLWH and in the general population.

Jesse Kwiek Awarded NIH R01 to Study Low Birth Weight and Mortality to Children Born to Mothers Living with HIV

Jesse Kwiek, Associate Professor, Department of Microbiology and CRR member, co-PI Marcel Yotebieng (Albert Einstein College of Medicine) and Co-Investigators Joan-Miquel Balada-Llasat (Ohio State), Nicholas Funderburg (Ohio State), Nichole Klatt (U of Minnesota), and Matt Sullivan (Ohio State) received a five-year NIH MPI R01 entitled "HIV/ART, Low Birth Weight (LBW), and Mortality in HIV-exposed Uninfected Children: A Translational Mechanistic Study."

To better understand how HIV/ART increases the risk of LBW, this study will use a well-characterized cohort of women living with HIV enrolled in a trial of data-driven continuous quality intervention to improve long term outcomes of ART in Kinshasa, Democratic Republic of Congo; the specific focus is on HIV-associated inflammation, immune activation, and microbial communities in the context of universal ART. A cohort of 600 women living with HIV on ART and 600 HIV-negative control along with their HIV-exposed uninfected (HEU) and HIV unexposed (HU) infants will be recruited and followed up through delivery and up to 12 months postpartum to determine how HIV/ART-induced placental dysfunction (Aim 1) or microbial dysbiosis (Aim 2) modulate the risk of LBW and subsequent infant mortality.

Using biological specimens obtained from those women, we will document histopathologic placental abnormalities (e.g. necrosis) and measure levels of markers of inflammation, immune activation and microbial translocation. Cutting-edge microbiome and virome toolkit with machine learning and ecosystem modeling approaches will be used to evaluate associations between these entities and inflammation and LBW, as well as in silico test myriad mechanistic hypotheses derived from functional analyses.

These studies will provide insight into the biological mechanism(s) associated with increased risk of LBW among HIV-exposed infants and could ultimately identify an optimal HIV treatment or care modality for pregnant WLH: one which promotes maternal health, prevents HIV mother-to-child transmission and maximizes infant survival.

Karin Musier-Forsyth Awarded NIH R21 to Investigate the Mechanism of Selective Packaging of Primer $tRNA^{Lys3}$ by HIV-1

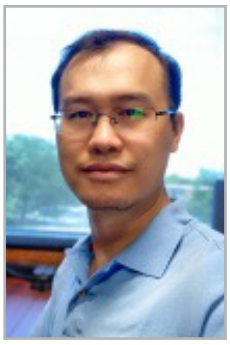
Karin Musier-Forsyth, PhD (Professor and Ohio Eminent Scholar, Department of Chemistry and Biochemistry) received a two-year, multi-PI R21 (Musier-Forsyth, Xiong) grant from NIH-National Institute of Allergy and Infectious Diseases to study HIV-1 packaging.

Retroviral life cycles show absolute dependence on a host tRNA for initiation of reverse transcription of the viral genome. HIV-1 primes reverse transcription with host $tRNA^{Lys3}$ and selectively enriches all $tRNA^{Lys3}$ isoacceptors in nascent virions at levels up to ten-fold higher than the cytoplasmic levels. This phenomenon of selective $tRNA^{Lys3}$ packaging by HIV-1 was identified nearly three decades ago but the underlying structural basis remains elusive to this day.

Several studies have established LysRS (lysyl-tRNA synthetase), the cognate cellular enzyme for aminoacylation of $tRNA^{Lys3}$, as a critical player in tRNA packaging by HIV-1.

The overall goal of this work is to establish a mechanistic and structural basis for selective packaging by (1) establishing the biochemical basis of the tRNA packaging complex formation; and (2) obtaining a high-resolution structure of the tRNA packaging complex.

Kai Xu Joins the Ohio State Faculty and Center for Retrovirus Research



Kai Xu, PhD was recruited to join the Department of Veterinary Biosciences in the College of Veterinary Medicine and the Center for Retrovirus Research. Dr. Xu received his doctoral degree at Cornell University in the laboratory of Dr. Dimitar Nikolov, where his dissertation focused on the structure and function of neuronal receptors and viral entry. As postdoctoral researcher in the laboratory of Dr. Peter Kwong at the Vaccine Research Center, he developed a new antibody-guided and structure-based strategy for HIV vaccine development.

Dr. Xu studied the structure and function of membrane fusion proteins, especially HIV-1 Env. He has applied rational design to HIV vaccine and invented a fusion peptide-based HIV vaccine that can induce broadly neutralizing antibodies in multiple animal experimental models including non-human primates. His studies have paved the way for the future development of effective HIV vaccine. The Xu lab will continue improve the efficacy of the HIV vaccine, as well as develop vaccines and immunotherapies for various other infectious pathogens, by incorporating recently developed technologies including nanoparticle epitope display, rapid affinity-matured nanobody generation, and multi-specificity antibody engineering.

Dr. Xu has actively worked on projects with several faculty members in the department, including Drs. Shan-Lu Liu, Amit Sharma, Jianrong Li and Prosper Boyaka. He is eagerly seeking collaboration with other members, as well as recruiting talented students and postdocs.

The Xu laboratory applies structural biology approaches (including X-ray crystallography and electron microscopy) to interpret viral glycoproteins and their interaction with host receptors and broadly protective antibodies. The goals of Dr. Xu's research are to broaden the understanding of the mechanism of viral entry and antibody protection and to provide structural and dynamic insights to assist in antiviral vaccine and drug development.

Welcome Kai!

The Center for Retrovirus Research

2021 Distinguished Research Career Award

Wei-Shau Hu, Ph.D was selected by the Center for Retrovirus Research of The Ohio State University to receive the 2021 Distinguished Research Career Award in recognition of her substantial body of work contributing to our understanding of retroviral recombination, RNA packaging and virus assembly.

Dr. Hu received her Ph.D. in Genetics from the University of California, Davis in 1987, where she studied the mechanisms of DNA recombination that lead to human α-thalassemia in Dr. James Shen's laboratory. Under Dr. Howard Temin's guidance, Dr. Hu studied the mechanisms of retroviral recombination as a postdoctoral fellow at the University of Wisconsin-Madison. Dr. Hu joined the faculty of West Virginia University in 1991 as an assistant professor in the Department of Microbiology and Immunobiology and the Mary Babb Randolph Cancer Center. She was promoted to associate professor with tenure in 1998. In 1999, she joined the National Cancer Institute (NCI) as Senior Investigator and Head of the Viral Recombination Section in the HIV Drug Resistance Program (renamed the HIV Dynamics and Replication Program in 2015).

Dr. Hu holds the 2021 Distinguished Career Award crystal.

Dr. Hu was an organizer of the 2009 Cold Spring Harbor Laboratory Retroviruses Meeting. She served as the Frederick representative of Women Science Advisors for the NCI from 2012 to 2016 and as a member of the AIDS Molecular and Cellular Biology Study Section of the National Institutes of Health extramural grant funding programs from 2010 to 2016. She currently serves as a member of the HIV Interactions in Viral Evolution (HIVE) Center, NCI Promotion Review Panel, and the steering committee of NCI RNA Biology Initiative.

Dr. Hu's research has been focused on HIV and she is an international leader in retroviral recombination, RNA packaging, and virus assembly, with numerous publications in outstanding journals, such as Science, PNAS, Molecular Cell, and PLoS Paths. Her innovations in combining molecular biology and biochemical approaches with state-of-the-art microscopy techniques for single-virion particle analysis have led to significant advancements in HIV molecular virology research. Dr. Hu was elected as a Fellow of American Academy of Microbiology in 2021.

Dr. Hu's distinguished award lecture was entitled "How Does HIV-1 Transfer Genetic Information to Its Progeny?" Her virtual visit was sponsored by the Center for Retrovirus Research, Department of Veterinary Biosciences, Infectious Disease Institute, and the Comprehensive Cancer Center.

Selected Grants and Recognitions

R01 HL158592-01 (**Funderburg**)
"Plaque and Blood Derived Macrophages: A Multi-omic Assessment of CVD Pathogenesis in PLWH" (2021-2024)

Ohio Cancer Research (**Panfil**)
"The Effects of m6A RNA Modifications on the Oncogenic Retrovirus HTLV-1" (2021-2022)

IDI Host Defense and Microbial Biology Grant Application Support (**Liyanage**) "Retooling NK Cells for an Effective HIV Vaccine" (2021-2022)

R01HD105526 (MPI: **Kwiek, Yotebieng**)
"HIV/ART, Low Birth Weight, and Mortality in HIV-Exposed Uninfected Children: A Translational Mechanistic Study" (2021-2026)

R21 AI157890-01 (MPI: **Musier-Forsyth, Xiong**)
"Mechanism of Selective Packaging of Primer $tRNA^{Lys3}$ by HIV-1" (2021-2023)

R35 GM141880 (PI: **Musier-Forsyth**)
"Translational Quality Control by Trans-editing Domains" (2021-2026)

U18 U18TR003807 (PI: **Reategui; Co-PI Liu**)
"Multi-parametric Integrated Molecular Detection of SARS-CoV-2 from Biofluids by Adapting Single Extracellular Vesicle Characterization Technologies" (2021-2022)

NIH T32 GM141955 (co-PI/PD: **Musier-Forsyth, Jackman**)
Cellular, Molecular and Biochemical Sciences Program (CMBP) Predoctoral training grant (2021-2026)

Young Investigator Award (**Liyanage**)
HIV Vaccine Trial Network, Early Stage Investigator conference, Portland, OR.

Microbial Infection & Immunity Pilot Grant (**Sharma**)
"Small molecule and macrocyclic peptide inhibitors for therapeutic targeting of SARS-CoV-2" (2021)

Patent: Inventors **Drs. Larue** and **Sharma** (Ohio State)
"Peptide Inhibitors for the Treatment and Prevention of Coronavirus Infections"

Patent: Inventors **Drs. Larue**, **Li**, **Foster**, and **Enming Xing** (Ohio State), **Dr. Gao**, **Wei Lou**, and **Shu Ning** (UCLA) "Bet Protein Inhibitors and Use Thereof"

2021 Graduates and Passage of Candidacy Exam

Shuohui Liu (Musier-Forsyth lab) successfully completed PhD

Jonathan Kitzrow (Musier-Forsyth lab) successfully completed PhD

Krithika Karthigeyan (Kwiek lab) successfully completed PhD

Danni Jin (Musier-Forsyth lab) successfully completed PhD

Yingke Tang (Musier-Forsyth lab) successfully completed PhD

Yehong Qiu (Musier-Forsyth lab) successfully passed candidacy

Christina Ross (Musier-Forsyth lab) successfully passed candidacy

Panke Qu (Liu Lab) successfully passed candidacy

Graduate Student, Post-doc, and Research Scientists Awards and Positions

Victoria Maksimova (Panfil Lab) was awarded a two-year Pelotonia Graduate Fellowship 2021-23

Shihyoung Kim (Kim Lab) was awarded a C. Glenn Barber stipend and tuition award 2021-22

Anna C Smith (Sharma Lab) was awarded a C. Glenn Barber stipend and tuition award 2021-23

Christina Ross (Musier-Forsyth lab) was awarded a CMBP T32 Fellowship 2021-22

Paola Loperena-Gonzalez (Kweik lab) was awarded a CMBP T32 Fellowship 2021-22

Manuja Gunasena (Liyanage Lab) 2021 CCTS Annual Meeting Poster Award

Manuja Gunasena (Liyanage Lab) IDI Fall 2021- Trainee Transformative Research Grant Award

Tatum Skladany (Liyanage Lab) 2021 Second-Year Transformational Experience Program (STEP) Award

Rajni Kant Shukla (Sharma Lab) IDI Trainee Transformative Research Grant "Developing Robust Methods for Noninvasive SIV Detection" 2021

Nicholas Chesarino (Sharma Lab) New Investigator Award from the University of Washington/Fred Hutch Center for AIDS Research (CFAR). 2021

Meetings

Viruses 2022: At the Leading Edge of Virology Research
April 5-8, 2022 (Virtual).
viruses2022.sciforum.net

20th International Conference on Human Retrovirology: HTLV and Related Viruses
May 8-11, 2022 Melbourne Australia (Virtual).
htlvconference2022.com/

Cold Spring Harbor Laboratory "Retroviruses"
May 23-28, 2022, Cold Spring Harbor, NY

32nd Workshop on Retroviral Pathogenesis
October 12-16, 2022, Vail, CO

Selected Publications

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