

RETRO-ACTIVE NEWS

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

2014 Highlights

The Center for Retrovirus Research 2014 Distinguished Research Career Award

Dr. David D. Ho, MD, founding Scientific Director and Chief Executive Officer of the Aaron Diamond AIDS Research Center and the Irene Diamond Professor at The Rockefeller University was the 15th recipient of the annual award for his seminal contributions to our understanding of HIV AIDS pathogenesis.



Dr. David Ho (left) receives Career Award crystal from Center for Retrovirus Research Director Dr. Patrick L. Green (right). Dr. Ho's Distinguished award lecture was entitled "New Approaches to HIV Prevention".

Dr. Ho received his degrees from California Institute of Technology (1974) and Harvard Medical School (1978). Subsequently, he did his clinical training in internal medicine and infectious diseases at Cedars-Sinai Medical Center/UCLA School of Medicine (1978-1982) and Massachusetts General Hospital/Harvard Medical School (1982-1985), respectively.

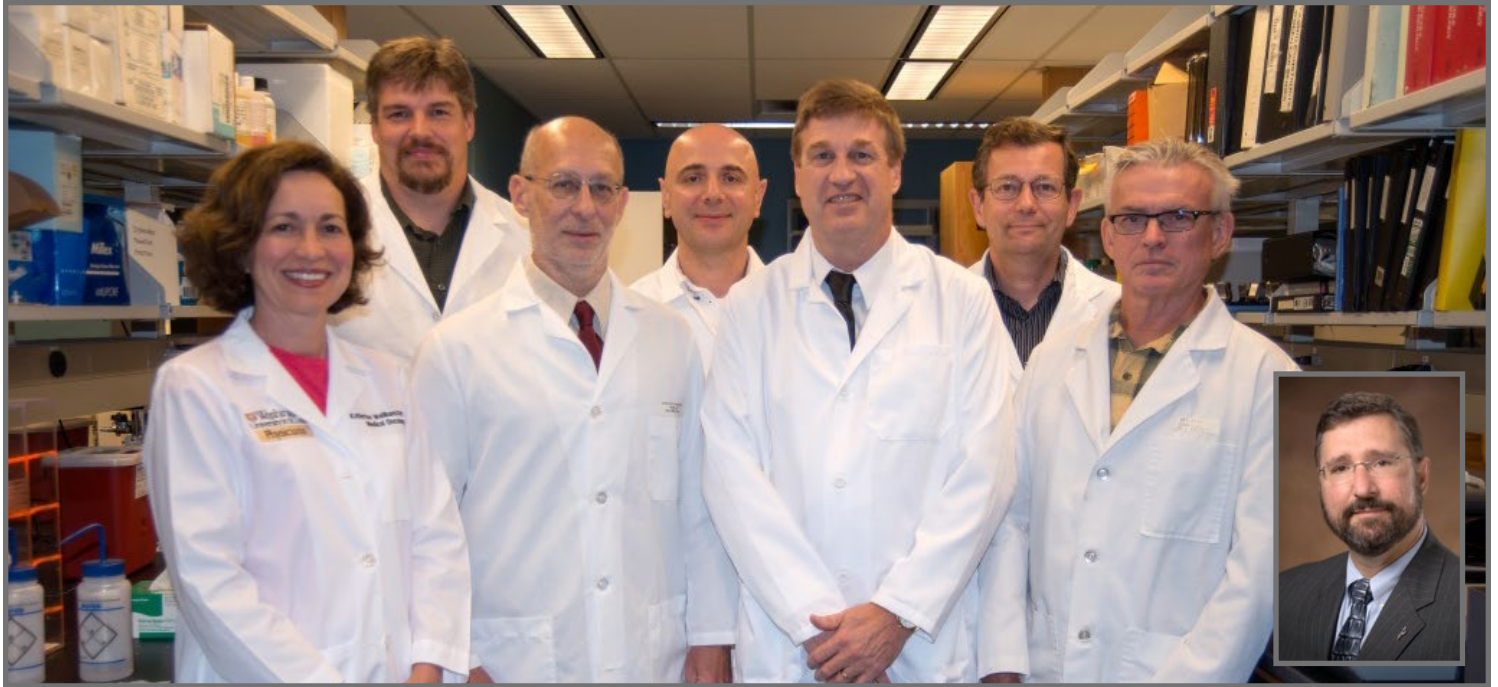
Dr. Ho has been at the forefront of AIDS research for 34 years, publishing over 350 papers. His elegant studies, beginning in 1994, unveiled the dynamic nature of HIV replication in vivo and revolutionized our basic understanding of AIDS. This knowledge led Dr. Ho to champion combination antiretroviral therapy that resulted in unprecedented control of HIV in patients. AIDS mortality in richer nations has declined 6-fold since 1996, and a massive international effort is now underway to bring such life-saving treatment to millions in the developing world. Dr. Ho's research team is now

devoting considerable efforts to develop vaccines to halt the spread of the AIDS epidemic. Furthermore, he is leading a consortium of Chinese and American organizations to help address the crisis of HIV/AIDS in China.

Dr. Ho has received numerous honors and awards for his scientific accomplishments. He is the recipient of 12 honorary doctorates. He has been chosen as the commencement speaker at Caltech, MIT, and Harvard School of Public Health. Additional accolades include the Ernst Jung Prize in Medicine, Mayor's Award for Excellence in Science & Technology, the Squibb Award, and the Hoechst Marion Roussel Award. Dr. Ho has been elected as a member of the American Academy of Arts and Sciences, Academia Sinica, Chinese Academy of Engineering, and the Institute of Medicine, National Academy of Science. He was a member of the Board of Overseers of Harvard University and is a board member of the MIT Corporation. Dr. Ho was named Time Magazine's Man of the Year in 1996, and was the recipient of a Presidential Medal in 2001. He was inducted into the California Hall of Fame in 2006.

Dr. Ho's visit was sponsored by the Center for Retrovirus Research, Departments of Veterinary Biosciences and Molecular Virology, Immunology and Medical Genetics, Public Health Preparedness for Infectious Diseases Program, Center for Microbial Interface Biology, and the Comprehensive Cancer Center.

Investigative team receives \$8.6 million NCI grant for the study of retrovirus-associated cancer

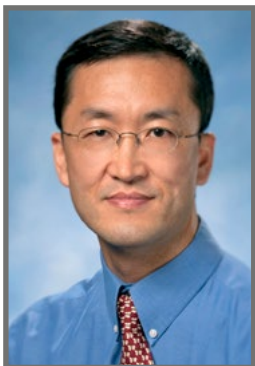


From left: Drs. Katherine Weilbaecher, Dan Rauch, Lee Ratner, Mamuka Kvaratskhelia, Patrick Green, Stefan Niewiesk, Lawrence Mathes, and Thomas Rosol

A multi-institutional investigative team of the Center for Retrovirus Research and members of the Ohio State University and Washington University Comprehensive Cancer Centers have been awarded a \$8.6 million program project grant (PPG) from the National Cancer Institute to investigate retroviral models of cancer (2014-2019). The ultimate goal of this PPG is to utilize the human T-cell leukemia virus type 1 (HTLV-1) T-cell immortalization model and the humanized immune system (HIS) mice or Tax transgenic mice to gain an understanding of how microenvironmental, cellular, and viral factors cooperate to promote development of cancer.

The findings will identify unique targets for diagnosis and treatment of HTLV-1 infection and adult T-cell leukemia and related leukemia/lymphoma. This grant is the third 5-year segment initially funded in 2003, which cumulatively totals more than \$29.5 million, making it the largest single grant in the college's history. The current team includes: Patrick Green (Program Director), Thomas Rosol, Stefan Niewiesk, Mamuka Kvaratskhelia, and Lawrence Mathes from Ohio State and, Katherine Weilbaecher and Lee Ratner from Washington University, St. Louis. Read more: vet.osu.edu/retrovirus-research/program-project-grant

Dr. Li Wu receives NIH/NCI award to explore the mechanisms of cutaneous T cell lymphoma



Dr. Li Wu, Professor and Center member has received a two-year grant of \$368,445 from the National Cancer Institute of the NIH. New findings from Dr. Wu's lab and colleagues in the Comprehensive Cancer Center suggest that a host enzyme called SAMHD1 may function as a tumor suppressor in cutaneous T cell lymphoma (CTCL).

In this project, Dr. Wu and his research team will test the hypothesis that silencing of SAMHD1 expression in malignant T-cells contributes to uncontrolled T-cell growth in CTCL. This project will provide critical knowledge into a novel mechanism regulating malignant CD4+ T-cell growth, which will facilitate the development of more effective drugs against CTCL and other T-cell lymphomas. This study can also be important in other types of cancer and have a broader impact in cancer biology.

Dr. Mamuka Kvaratskhelia receives NIH/NIAID R01 to discover new types of allosteric HIV-1 integrase inhibitors



The principal objective of Dr Kvaratskhelia's studies is to impair integrase (IN) function by stabilizing rather than destabilizing interacting IN subunits to promote aberrant protein multimerization. The group has demonstrated that a small molecule can inhibit IN catalytic activity in vitro by binding at the protein dimer interface, stabilizing the interacting subunits and promoting formation of higher-order oligomers.

The research is designed to rationally develop multimeric HIV-1 IN inhibitors (MINIs) and elucidate their antiviral mechanism of action; they will also investigate IN resistance mutations that arise from treatment of HIV-1 in cell culture with MINIs and develop second generation inhibitors; lastly they will focus on discovery of new MINIs through high-throughput screening (HTS) of a library of compounds and subsequent hit-to-lead optimization. These MINIs are expected to target previously unexploited sites on HIV-1 IN and potentially inhibit HIV-1 phenotypes resistant to all currently used highly active antiretroviral therapy.

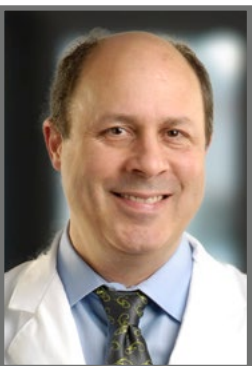
Drs. Green and Baiocchi funded to explore the role of protein arginine methyltransferase 5 in T-cell transformation and disease

Drs. Patrick Green (Center member) and Robert Baiocchi,



MD/PhD (Comprehensive Cancer Center) have been awarded a NIH/NIAID R21 exploratory grant to investigate the role of protein arginine methyltransferase 5 (PRMT5) in T-cell transformation and disease. PRMT5 is involved in a wide variety of cellular processes, including RNA processing, transcriptional regulation and signal transduction pathways that

are highly relevant to the pathogenesis of cancer. The team hypothesized that 1) PRMT5 over-expression would be relevant to HTLV-1-driven T cell transformation and



2) inhibitors of PRMT5 activity (PRMT5i) would provide a novel approach capable of targeting a newly discovered oncogenic pathway and lead to improved strategies to treat patients with adult T-cell leukemia (ATL) and other related cancers. Thus far, the group has identified PRMT5 as a potential target to modulate HTLV-1 gene expression; a decrease in

cell proliferation and in viral gene expression is observed when PRMT5 is knocked down or inhibited in HTLV-1-infected/-transformed cells.

2014 Graduates

Nathan Dissinger, PhD (Green Lab)

"In vitro functional comparisons of HTLV-1 HBZ and HTLV-2 APH-2: Implications for viral persistence and pathobiology" Accepted a post-doctoral fellowship position at University of North Carolina.

Jessy Mates, PhD (Kwiek Lab)

"Transcriptional regulation of HIV-1" NIH T32 post-doctoral fellow at The Ohio State University

Tiffany Rye-McCurdy, PhD (Musier-Forsyth Lab)

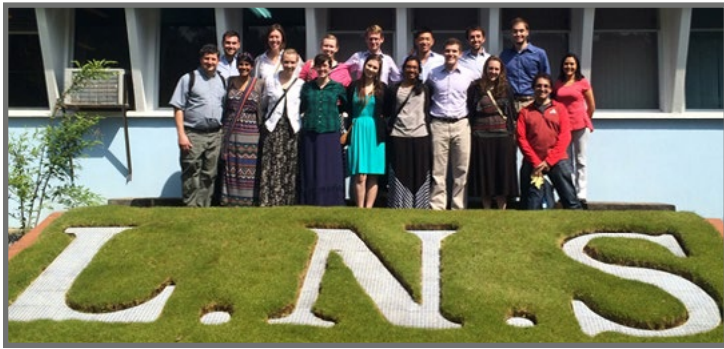
"The role of Rous sarcoma virus Gag in tRNA primer annealing and genomic RNA encapsidation" Accepted a post-doctoral fellowship position at The Ohio State University.

Jonathan Roger, MS (Wu Lab)

"Non-POU domain-containing octamer-binding protein negatively regulates HIV-1 infection in CD4+ T-cells" Current Position: Research Technician, Nationwide Children's Hospital Research Institute.

Dr. Jesse Kwiek organized an infectious disease education mission to Guatemala.

During the autumn semester of their senior year, Ohio State Biomedical Science (BMS) Students enroll in BMS4810h course “Special Topics in BMS: Immunology and Infectious Diseases,” co-directed by Drs. Jesse Kwiek and Jordi Torrelles. This course focuses on infectious diseases, specifically HIV and tuberculosis (TB). As part of the course, 15 students completed a 10-day service learning project in Xela, Guatemala, where they partnered with several local community organizations whose missions focus on the HIV and TB epidemics. For additional information, please visit lsn.osu.edu/news/students-apply-classroom-concepts-real-world-problems.



Student, Post-doc, and Research Scientist Awards

Jenna Antonucci (Wu Lab)
HHMI Med into Grad Fellowship

Jacob Al-Saleem (Green Lab)
C. Glenn Barber Research Grant
(stipend & tuition)

Corine St.Gelais, PhD (Wu Lab)
promoted to Senior Research Associate

Mitchell Peake, undergraduate (Yoder Lab)
SOLAR Foundation Research Award

Molly Osterhage, undergraduate (Yoder Lab)
OSU Undergraduate Research Scholarship

Jacob Al-Saleem (Green Lab)
CVM Research Day, First Place research poster
presentation

Nathan Titkemeier (Musier-Forsyth Lab)
HHMI Med into Grad Fellowship

Selected Upcoming Meetings

Viruses and Human Cancer March 29-April 3, Big Sky, MT

Cold Spring Harbor Laboratory “Retroviruses” May 18-23, 2015, Cold Spring Harbor, NY

American Society for Microbiology May 30-June 2, 2015, New Orleans, LA

17th International Conference on Retrovirology: HTLV & Related Viruses June 18-22, 2015, Martinique

American Society for Virology July 11-15, 2015, London/Ontario, Canada

27th Workshop on Retroviral Pathogenesis August 24-27, 2015, Mülheim an der Ruhr, Germany

Selected Grant Awards

Nicholas Funderburg, NIH R56HL126563 “Cellular mediators of vascular inflammation in treated HIV disease” (2014-2015)

Mamuka Kvaratskhelia, NIH/NIAID R01 AI110310 “Multimeric HIV-1 Integrase Inhibitors” (2014-2019)

Karin Musier-Forsyth, NIH/NIGMS R01GM113887 “Cellular Factors Critical for Initiation of HIV-1 Reverse Transcription” (2014-2018)

Li Wu, NIH/NCI, R21 CA181997 “Novel Role of SAMHD1 as a Tumor Suppressor in Cutaneous T-cell Lymphomas” (2014-2016)

Patrick Green (Program Director), Thomas Rosol, Stefan Niewiesk, Mamuka Kvaratskhelia, NIH/NCI P01 CA100730 “Retrovirus Models of Cancer” (2014-2019)

Karin Musier-Forsyth NIH P50 HIV Center Collaborative Development Proposal (PI;Olson) Project “Characterization of HIV-1 reverse transcription initiation” (2014-2016)

Patrick Green, NIH/NIAID R21 AI111125 “The Role of PRMT5 in HTLV-1 Transformation and Disease” (2014-2016)

Mamuka Kvaratskhelia, NIH/NIAID R21 AI109522 “Cellular Cofactors of Murine Leukemia Virus Integrase” (2014-2016)

Jesse Kwiek, Esanex Inc, “Mechanism of action of SNX-2112” (2014-2015).

Selected Publications

Bennett, G, Peters R, Wang X, Hanne J, Sobol RW, Bundschuh R, Fishel R, **Yoder KE**. Repair of oxidative DNA base damage in the host genome influences the HIV integration site sequence preference. *PLoS ONE*. 2014, 9:e103164

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Funderburg NT. Markers of coagulation and inflammation often remain elevated in ART-treated HIV-infected patients. *Curr Opin HIV AIDS*. 2014 Jan;9(1):80-6.

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Parrula C, Fernandez S, **Landes K**, Huey D, Lairmore MD, **Niewiesk S**. Success of measles virotherapy in ATL depends on type I interferon secretion and responsiveness. *Virus Research* 2014 189, 206-213.

Rye-McCurdy TD, Nadaraia-Hoke S, Gudleski-O'Regan N, Flanagan JM, Parent LJ, **Musier-Forsyth K**. Mechanistic Differences Between Nucleic Acid Chaperone Activities of the Gag Proteins of RSV and HIV-1 are Attributed to the MA Domain. *J Virology*, 2014 88(14):7852-61

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