

# RETRO-ACTIVE NEWS

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

## 2013 Highlights

### The Center for Retrovirus Research 2013 Distinguished Research Career Award

Dr. Anna Marie (Ann) Skalka PhD. Professor and W. W. Smith Chair in Cancer Research, Senior Advisor to the President, Fox Chase Cancer Center, Philadelphia, PA was the 14th recipient of the annual award for her seminal contributions to our understanding of the biochemical mechanisms by which retroviruses (including HIV) replicate and insert their genetic material into the host genome.



Dr. Anna Marie Skalka (center) receives Career Award crystal from Center for Retrovirus Research Director Dr. Patrick L. Green (right) and Center member Dr. Mamuka Kvaratskhelia (left). Distinguished award lecture entitled "Deciphering the Anatomy of a DNA Invasion Machine: the Retroviral Integrases".

Dr. Skalka obtained her Ph.D. degree in Microbiology from New York University Medical School with Dr. Jerard Hurwitz, and was a postdoctoral fellow with Nobel Laureate, Dr. Alfred Hershey, at the Carnegie Institution in Cold Spring Harbor. She continued her scientific career at Roche Institute of Molecular Biology and Hoffmann-La Roche, Inc., where she held several key positions including Head of Department of Molecular Oncology at Roche Institute of Molecular Biology, and Assistant Vice President of Hoffmann-La Roche, Inc. Since 1987, Dr. Skalka has been a Professor and the W. W. Smith Chair in Cancer Research at the Fox Chase Cancer Center. She also served as Senior Vice President for Basic Science from 1987 until 2008.

Dr. Skalka's major research interests are the molecular aspects of the replication of retroviruses. Dr. Skalka's recent work has focused on elucidating the architecture of a key retroviral enzyme, integrase, and has provided critical information for both understanding the function

of this protein as well as exploiting it as a therapeutic target. Dr. Skalka has published more than 240 scientific papers and scholarly reviews, has edited several scientific books, organized and spoken at national and international meetings and conferences, and is coauthor of the widely acclaimed textbook, Principles of Virology.

Dr. Skalka has served on the editorial boards of several peer-reviewed scientific journals and has been a member of numerous advisory boards, including the National Cancer Institute Board of Scientific Counselors, the General Motors Cancer Research Foundation Awards Assembly, the Board of Governors of the American Academy of Microbiology, and the National Advisory Committee for the Pew Biomedical Scholars Program. Dr. Skalka has also been deeply involved in state, national, and international advisory groups concerned with the broader, societal implications of scientific research; including chairing the NJ Commission on Cancer Research. In recognition of her outstanding research accomplishments, she has been elected to the American Academy of Arts and Sciences, the American Association for the Advancement of Science, and to the Board of Governors of the American Academy of Microbiology.

Dr. Skalka'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, and the Comprehensive Cancer Center Viral Oncology Program.



## Dr. Li Wu Receives NIH Award to Study HIV-1 Restriction



Dr. Li Wu, Associate Professor and Center member has received a four-year R01 award from the NIH in a total amount of \$1,515,725 to investigate the mechanisms of HIV-1 restriction in dendritic cells (DCs). Immune activation is the driving force of HIV-1 replication, which facilitates viral infection in target cells and fundamentally contributes to AIDS pathogenesis. Myeloid cells, including monocytes, DCs, and macrophages, play a critical role in innate immunity

against viral infection. Dr. Wu's long-term goal is to define the mechanisms regulating immune activation of myeloid cells during HIV-1 infection. SAMHD1 is an HIV-1 restriction factor in myeloid cells and has been proposed to act as a negative regulator of the interferon response. In this project, Dr. Wu and his colleagues aim to study the mechanisms of SAMHD1-mediated HIV-1 restriction in DCs and the role of SAMHD1 in regulating immune activation of DCs. These studies will provide new insights into intrinsic immunity against HIV-1 infection in myeloid DCs, which can help develop novel interventions to block HIV-1 infection and transmission.

## Dr. Mamuka Kvaratskhelia's Laboratory and a Multi-Institution Team of Scientists Identify Bromodomain and Extraterminal Domain (Bet) Proteins as Key Cofactors in Efficient Murine Leukemia Virus Integration and Targeting



The selection of chromosomal targets for retroviral integration varies markedly, tracking with the genus of the retrovirus, suggestive of targeting by binding to cellular factors. Integration site mapping reveals that  $\gamma$ -retroviral murine leukemia virus (MLV) DNA integration into the host genome is favored at transcription start sites, but the underlying mechanism for this preference is unknown. Dr. Kvaratskhelia's research group in collaboration with other Center for Retrovirus Research investigators (L.Wu, and P.Green) and colleagues at University of Pennsylvania (F.Bushman) and Robert Wood Johnson Medical School (M.Roth) have identified bromodomain and extraterminal domain (BET) proteins (Brd2, -3, -4)

as cellular-binding partners of MLV integrase. The primary authors of the study were Drs. A. Sharma and R. Larue. These researchers have shown that purified recombinant Brd4(1-720) binds with high affinity to MLV integrase and stimulates correct concerted integration in vitro. Moreover JQ-1, a small molecule that selectively inhibits interactions of BET proteins with modified histone sites, impaired MLV but not HIV-1 integration in infected cells. Comparison of the distribution of BET protein-binding sites analyzed using ChIP-Seq data and MLV-integration sites revealed significant positive correlations. Antagonism of BET proteins, via JQ-1 treatment or RNA interference, reduced MLV-integration frequencies at transcription start sites. These findings elucidate the importance of BET proteins for MLV integration efficiency and targeting and provide a route to developing safer MLV-based vectors for human gene therapy.

### Selected Grant Awards

William Cantera (Musier-Forsyth) - Pelotonia Postdoctoral Fellowship

Li Wu, NIH R01AI104483-01 "Mechanisms of SAMHD1-mediated HIV-1 Restriction in Dendritic Cells" (2013-2017)

Li Wu, CMIB and Arno Therapeutics "Evaluation of anti-HIV activity of AR-12 and its derivatives and effect of AR-42 on HIV latency in CD4+ T-cells" (2013-2015)

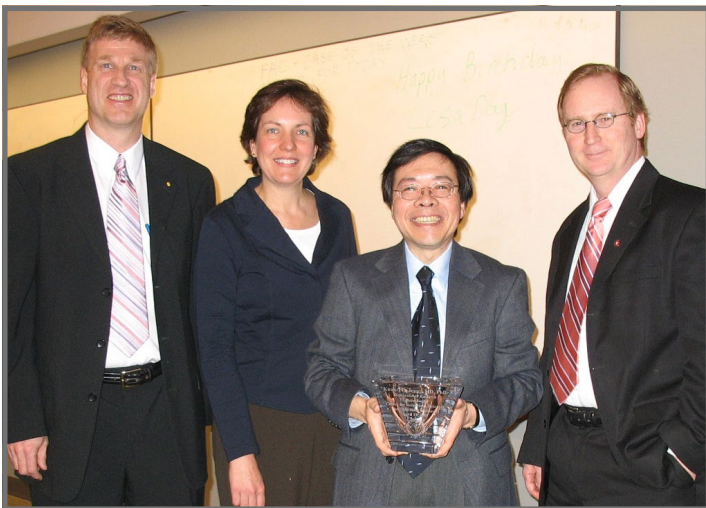
Annette Ratcliff (Kwiek) - Pelotonia Postdoctoral Fellowship

Li Wu, Natural Science Foundation of China (NSFC) "Mechanisms of the Gain and Loss of the vpx Gene in Primate Lentiviruses" (2013-2015)

## Retrovirology Loses Kuan-Teh Jeang

On January 27, 2013 we unexpectedly lost our scientific colleague and advisor, Kuan-Teh Jeang, M.D., Ph.D.

“Teh was a dynamic scientist, an effective teacher, a mentor, a highly successful journal editor, and an inspiring leader. He was generous with his time at so many levels” (Patrick Green). “Teh was unique in his energy and drive, along with intellect. Teh did not follow, he led with unrelenting forcefulness.” (Kathleen Boris-Lawrie). “Teh was the ultimate skeptic and brilliant interrogator of science. He added a wonderful ability to ask the right question at the right time.” (Michael Lairmore).



Kuan-Teh Jeang receives the 2007 Ohio State Center for Retrovirus Research Distinguished Career Award (from left, Drs. Patrick Green, Kathleen Boris-Lawrie, Kuan-Teh Jeang, and Michael Lairmore)

Teh served as advisor to the Center for Retrovirus Research and as chair of the external advisory board of our NIH/NCI program project grant for nearly a decade (a joint venture between Ohio State University and Washington University). Those of us who were lucky enough to have his time on the review reaped the benefit of his insightfulness and critique. Teh was also presented with the 2007 Ohio State University Center for Retrovirus Research Distinguished Career Award for his significant contributions to the fields of HIV and HTLV biology.

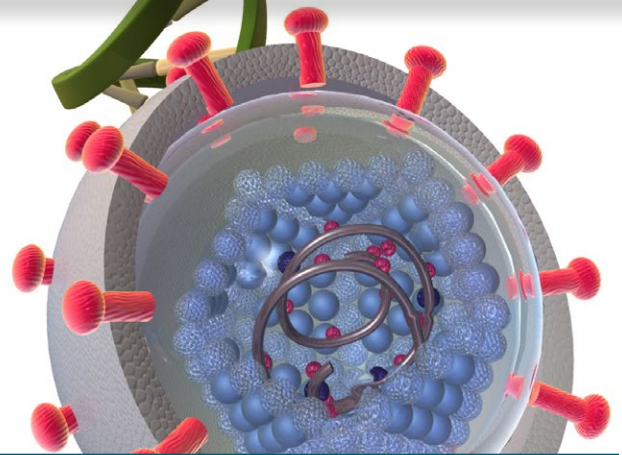
Our dear colleague and friend will be missed.

See the following links for more detail:

<http://www.retrovirology.com/content/10/1/28> or  
<http://jvi.asm.org/content/87/12/6539.full>

### Doctoral Graduate

Jocelyn O. Eidahl, PhD (Kvaratskhelia)  
“Characterizing interactions between the cellular HIV-1 integration cofactor, LEDGF/p75 with chromatin and HIV-1 integrase”



### Student, Post-doc, and Research Scientist Awards

Dr. Suresh de Silva (Wu) - CMIB Retreat First Place of Travel Award for Short Talk Presentation.

Molly Osterhage (Yoder) - Mayers Summer Research Scholarship and a SOLAR Fund Undergraduate Research Award

Erik Olson (Musier-Forsyth) - NIH Chemical-Biology Interface Predoctoral Training Grant Fellowship

Dr. Corine St.Gelais (Wu) - PHPID travel award to attend CSH International Meeting on Retroviruses.

Alice Ducon (Musie-Forsyth) - RNA Center Predoctoral Fellowship

Dr. Amanda R. Panfil (Green) – NIH T32 Cancer Genetics Training Grant Fellowship

Feifei Wang (Wu) – C. Glenn Barber Fellowship

Nathan Dissinger (Green) - American Society of Virology Travel Award



## Selected publications

- Anapum R, Doueiri R, **Green PL**. The need to accessorize: Molecular roles of HTLV-1 p30 and 1 HTLV-2 p28 accessory proteins in the viral life cycle. *Frontiers in Virology*, 2013, Sep 17;4:275.
- Chen CY, Liu X, **Boris-Lawrie K**, Sharma A, Jeang KT. Cellular RNA helicases and HIV-1: insights from genome-wide, proteomic, and molecular studies. *Virus Research* 2013 Feb;171(2):357-65. doi: 10.1016/j.virusres.2012.06.022.
- Coleman CM, St. Gelaics C, **Wu L**. Cellular and viral mechanisms of HIV-1 transmission mediated by dendritic cells. In *HIV Interactions with Dendritic Cells: Infection and Immunity*. Edited by **Wu L**. and Schwartz O. Springer, New York. September 2013.
- de Silva S, Hoy H, Hake TS, Wong HK, Porcu P, **Wu L**. Promoter methylation regulates SAMHD1 gene expression in human CD4+ T cells. *J Biol Chem* 2013, 288(13): 92849292.
- Dewan V, Reader J, **Musier-Forsyth K**. Role of aminoacyl-tRNA synthetases in infectious diseases and targets for therapeutic development. In *Topics in Current Chemistry* (Ed. Sunghoon Kim), Springer Verlag, 2013.
- Dong C, Zhao G, Zhong M, Yue Y, **Wu L**, Xiong S. RNA sequencing and transcriptomal analysis of human monocyte to macrophage differentiation. *Gene* 2013, 519 (2): 279-287.
- Eidahl JO, Crowe BL, North JA, McKee CJ, Shkriabai N, Feng L, Plumb M, Graham RL, Gorelick RJ, Hess S, Poirier MG, Foster MP, **Kvaratskhelia M**. Structural basis for high-affinity binding of LEDGF PWWP to mononucleosomes. *Nucleic Acids Res* 2013 Apr 1;41(6):3924-36.
- Engelman A, Kessler JJ, **Kvaratskhelia M**. Allosteric inhibition of HIV-1 integrase activity. *Curr Opin Chem Biol* 2013 Jun;17(3):339-45.
- Enose-Akahata Y, Abrams A, Massoud R, Bialuk I, **Green PL**, Maloney EM, Jacobson S. Humoral immune response to HTLV-1 basic leucine zipper factor (HBZ) in HTLV-1-infected individuals. *Retrovirology* 2013, 10(1):19.
- Feng L, Sharma A, Slaughter A, Jena N, Koh Y, Shkriabai N, Larue RC, Patel PA, Mitsuya H, Kessler JJ, Engelman A, Fuchs JR, **Kvaratskhelia M**. The A128T resistance mutation reveals aberrant protein multimerization as the primary mechanism of action of allosteric HIV-1 integrase inhibitors. *J Biol Chem* 2013 May 31;288(22):15813-20.
- Jones CP, Saadatmand J, Kleiman L, **Musier-Forsyth K**. Molecular mimicry of human tRNA<sup>Lys</sup> anticodon by HIV-1 RNA genome facilitates viral replication. *RNA* 2013, 19(2): 219-29.
- Jurado KA, Wang H, Slaughter A, Feng L, Kessler JJ, Koh Y, Wang W, Ballandras-Colas A, Patel PA, Fuchs JR, **Kvaratskhelia M**, Engelman A. Allosteric integrase inhibitor potency is determined through the inhibition of HIV-1 particle maturation. *Proc Natl Acad Sci U S A* 2013 May 21;110(21):8690-5. doi: 10.1073/pnas.1300703110.
- Kannian P, Fernandez S, Jones KS **Green PL**. Human T lymphotropic virus type 1 (HTLV-1) SU residue 195 plays a role in determining the preferential CD4+ T cell transformation/transformation tropism. *J Virology* 2013, Aug;87(16):9344-9352.
- Mates JM, Kumar SB, Bazan J, Mefford M, Voronkin I, Handelman S, Mwapasa V, Ackerman W 4th, Janies D, **Kwiek JJ**. Genotypic and Phenotypic Heterogeneity in the U3R Region of HIV Type 1 Subtype C. *AIDS Res Hum Retroviruses*. 2013 Aug 12. [Epub ahead of print]
- Mitra M, Wang W, Vo M-N, Rouzina I, Barany G, **Musier-Forsyth K**. The N-terminal zinc finger and flanking basic domains represent the minimal region of HIV-1 nucleocapsid protein for targeting chaperone function. *Biochemistry* 2013, 52(46): 8226-36.
- Sharma A, Larue RC, Plumb MR, Malani N, Slaughter A, Kessler JJ, Shkriabai N, Aiyer SS, **Green PL**, **Wu L**, Roth MJ, Bushman FD, **Kvaratskhelia M**. BET proteins promote efficient murine leukemia virus integration at transcription start sites. *Proc Natl Acad Sci U S A*, 2013, Jul 16;110(29):12036-41.
- Turner AN, Tabbah S, Mwapasa V, Rogerson SJ, Meshnick SR, Ackerman WE 4th, **Kwiek JJ**. Severity of maternal HIV-1 disease is associated with adverse birth outcomes in Malawian women: a cohort study. *J Acquir Immune Defic Syndr* 2013 Dec 1;64(4):392-9.
- Webb J, Jones CP, Parent LJ, Rouzina I, **Musier-Forsyth K**. Distinct binding interactions of HIV-1 Gag to Psi and non-Psi RNAs: Implications for viral genomic RNA packaging. *RNA* 2013, 19(8):1078-88.
- Wu L**. Samhd1 knockout mice: modeling retrovirus restriction in vivo. *Retrovirology* 2013, 10:142.
- Wu H, Mitra M, McCauley MJ, Thomas JA, Rouzina I, **Musier-Forsyth K**, Williams MC, Gorelick RJ. Aromatic residue mutations reveal direct correlation between HIV-1 nucleocapsid protein's nucleic acid chaperone activity and retroviral replication. *Virus Research* 2013, 171(2): 263-277.
- Zhai RR, Jiang AP, Ma L, Ren XX, Jiang JF, **Wu L**, Wei JF, Wang JH. Histamine enhances HIV-1-induced modulation of dendritic cells to skew naive T cell differentiation toward regulatory T cells. *Virology* 2013, 442(2):163-172.