BIOGRAPHICAL SKETCH

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NAME: Tilton, John

eRA COMMONS USER NAME (credential, e.g., agency login):

POSITION TITLE: Assistant Professor, Department of Nutrition and Center for Proteomics and Bioinformatics

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Princeton University, Princeton, NJ	AB	05/1995	Molecular Biology
Yale University School of Medicine, New Haven, CT	MD	05/2001	Medicine

A. Personal Statement

The research in my laboratory is aimed at identifying cellular factors that are required for HIV infection of target cells. In the context of HIV, we seek to block interactions between viral proteins and key cellular dependency factors and thereby diminish HIV infection. For instance, we have recently demonstrated that the histone deacetylase (HDAC) inhibitor vorinostat (SAHA) can increase the susceptibility of uninfected CD4+ T cells to HIV infection. This phenomenon appears to be dependent on the inhibition of cytoplasmic HDACs leading to the acetylation of tubulin, which results in enhancement of stable microtubules that are utilized by the virus to traffic from the plasma membrane to the nucleus. Vorinostat enhances post-entry events in HIV infection including reverse transcription, nuclear import, and integration. This previously unknown effect of HDACs on HIV infection is of clinical importance because vorinostat is being evaluated as a latency-reversing agent in human subjects as a potential component of strategies to eradicate latent reservoirs and cure HIV infection. Our results indicate that these agents will need to be used in the setting of effective antiretroviral therapy to block new infections and indicate that class I HDAC inhibitors that act primarily in the nucleus may be able to reverse latency without affecting tubulin and increasing the risk of seeding new reservoirs. In addition, my laboratory has a strong interest in HIV cure, including questions about which cellular subsets are reservoirs for HIV, which pathways are most effective at inducing HIV out of latency in different cell types, and practical strategies to eliminate HIV reservoirs in patients.

B. Positions and Honors

Positions and Employment

1999 - 2000 HHMI-NIH Cloisters Research Scholar, National Institutes of Health, Bethesda, MD
2001 - 2006 Clinical Research Fellow, Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, Bethesda, MD
2006 - 2010 Senior Research Investigator, Department of Microbiology, University of Pennsylvania, Philadelphia, PA
2010 - Assistant Professor, Department of Nutrition and Center for Proteomics and Bioinformatics, Case Western Reserve University, Cleveland, OH
2012 - Director of Immunobiology, Center for Proteomics and Bioinformatics, Case Western Reserve University, Cleveland, OH

Other Experience and Professional Memberships

2014 - Member, American Society for Microbiology

Honors

1995	Magna Cum Laude, Princeton University
1995	Sigma Xi Scientific Research Society, Princeton University
1998	Winternitz Prize in Pathology, Yale University School of Medicine
2000	HHMI-NIH Research Scholar, Howard Hughes Medical Institute
2002	Special Act Award, National Institutes of Health
2003	Special Act Award, National Institutes of Health
2004	Special Act Award, National Institutes of Health
2005	Special Act Award, National Institutes of Health
2007	Ruth L. Kirschstein National Research Service Award, National Institutes of Health
2008	Postdoctoral Speaking Award, University of Pennsylvania

C. Contribution to Science

1. Cellular immune responses in HIV-infected patients: My early publications, while working for Mark Connors, M.D., in the Laboratory of Immunoregulation at the NIAID/NIH, focused on cellular immune responses to viral infections in patients with or without HIV infection. In multiple cell types - CD4+ T cells, monocytes, and dendritic cells - we observed an effect where HIV viremia was associated with impaired immune function, including proliferative defects and altered cytokine profiles.

    a. Iyasere C, Tilton JC, Johnson AJ, Younes S, Yassine-Diab B, Sekaly RP, Kwok WW, Migueles SA, Laborico AC, Shupert WL, Hallahan CW, Davey RT Jr, Dybul M, Vogel S, Metcalf J, Connors M. Diminished proliferation of human immunodeficiency virus-specific CD4+ T cells is associated with diminished interleukin-2 (IL-2) production and is recovered by exogenous IL-2. J Virol. 2003 Oct;77(20):10900-9. PubMed PMID: 14512540; PubMed Central PMCID: PMC224997.

    b. Tilton JC, Johnson AJ, Luskin MR, Manion MM, Yang J, Adelsberger JW, Lempicki RA, Hallahan CW, McLaughlin M, Mican JM, Metcalf JA, Iyasere C, Connors M. Diminished production of monocyte proinflammatory cytokines during human immunodeficiency virus viremia is mediated by type I interferons. J Virol. 2006 Dec;80(23):11486-97. PubMed PMID: 17005663; PubMed Central PMCID: PMC1642603.

    c. Tilton JC, Luskin MR, Johnson AJ, Manion M, Hallahan CW, Metcalf JA, McLaughlin M, Davey RT Jr, Connors M. Changes in paracrine interleukin-2 requirement, CCR7 expression, frequency, and cytokine secretion of human immunodeficiency virus-specific CD4+ T cells are a consequence of antigen load. J Virol. 2007 Mar;81(6):2713-25. PubMed PMID: 17182676; PubMed Central PMCID: PMC1865970.

    d. Tilton JC, Manion MM, Luskin MR, Johnson AJ, Patamawenu AA, Hallahan CW, Cogliano-Shutta NA, Mican JM, Davey RT Jr, Kottilil S, Lifson JD, Metcalf JA, Lempicki RA, Connors M. Human immunodeficiency virus viremia induces plasmacytoid dendritic cell activation in vivo and diminished alpha interferon production in vitro. J Virol. 2008 Apr;82(8):3997-4006. PubMed PMID: 18256146; PubMed Central PMCID: PMC2293017.

2. Viral resistance to CCR5 inhibitors in patients: With Robert Doms, M.D. Ph.D., at the University of Pennsylvania, I explored viral resistance to the CCR5 antagonists maraviroc and aplaviroc in patients treated with these drugs. Our work helped establish the finding that viruses can utilize drug-bound CCR5 as a mechanism of resistance and that these resistant viruses can be pre-existing in patients. Additionally, we discovered that the interactions between the HIV gp120 protein and drug-bound CCR5 can influence the degree of cross-resistance to other CCR5 antagonists.

    a. Tilton JC, Amrine-Madsen H, Miamidian JL, Kitrinos KM, Pfaff J, Demarest JF, Ray N, Jeffrey JL, Labranche CC, Doms RW. HIV type 1 from a patient with baseline resistance to CCR5 antagonists uses drug-bound receptor for entry. AIDS Res Hum Retroviruses. 2010 Jan;26(1):13-24. PubMed PMID: 20055594; PubMed Central PMCID: PMC2858898.

    b. Pfaff JM, Wilen CB, Harrison JE, Demarest JF, Lee B, Doms RW, Tilton JC. HIV-1 resistance to CCR5 antagonists associated with highly efficient use of CCR5 and altered tropism on primary

CD4+ T cells. J Virol. 2010 Jul;84(13):6505-14. PubMed PMID: 20410277; PubMed Central PMCID: PMC2903254.

c. Tilton JC, Wilen CB, Didigu CA, Sinha R, Harrison JE, Agrawal-Gamse C, Henning EA, Bushman FD, Martin JN, Deeks SG, Doms RW. A maraviroc-resistant HIV-1 with narrow cross-resistance to other CCR5 antagonists depends on both N-terminal and extracellular loop domains of drug-bound CCR5. J Virol. 2010 Oct;84(20):10863-76. PubMed PMID: 20702642; PubMed Central PMCID: PMC2950574.

d. Lobritz MA, Ratcliff AN, Marozsan AJ, Dudley DM, Tilton JC, Arts EJ. Multifaceted mechanisms of HIV inhibition and resistance to CCR5 inhibitors PSC-RANTES and Maraviroc. Antimicrob Agents Chemother. 2013 Jun;57(6):2640-50. PubMed PMID: 23529732; PubMed Central PMCID: PMC3716150.

3. Cellular susceptibility to HIV infection: In my current laboratory at Case Western Reserve University, we have established a combination reporter virus assay that allows monitoring of viral fusion and LTR-driven EGFP production - a surrogate of productive infection - to investigate (a) types of cells susceptible to HIV and (b) cellular proteins that regulate susceptibility. These efforts have led to the identification of a novel target cell for HIV, the memory stem cell (Tscm) as well as identified histone deacetylase 6 (HDAC6) as a regulator of cellular susceptibility to infection.

a. Haqqani AA, Marek SL, Kumar J, Davenport M, Wang H, Tilton JC. Central memory CD4+ T cells are preferential targets of double infection by HIV-1. Virol J. 2015 Nov 11;12:184. PubMed PMID: 26559763; PubMed Central PMCID: PMC4642630.

b. Lucera MB, Tilton CA, Mao H, Dobrowolski C, Tabler CO, Haqqani AA, Karn J, Tilton JC. The histone deacetylase inhibitor vorinostat (SAHA) increases the susceptibility of uninfected CD4+ T cells to HIV by increasing the kinetics and efficiency of postentry viral events. J Virol. 2014 Sep;88(18):10803-12. PubMed PMID: 25008921; PubMed Central PMCID: PMC4178860.

c. Tabler CO, Lucera MB, Haqqani AA, McDonald DJ, Migueles SA, Connors M, Tilton JC. CD4+ memory stem cells are infected by HIV-1 in a manner regulated in part by SAMHD1 expression. J Virol. 2014 May;88(9):4976-86. PubMed PMID: 24554663; PubMed Central PMCID: PMC3993838.

d. Tilton CA, Tabler CO, Lucera MB, Marek SL, Haqqani AA, Tilton JC. A combination HIV reporter virus system for measuring post-entry event efficiency and viral outcome in primary CD4+ T cell subsets. J Virol Methods. 2014 Jan;195:164-9. PubMed PMID: 24025341; PubMed Central PMCID: PMC3982591.

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

R01 HD077886-03 Tilton, John Christian (PI) 09/13/13-05/31/18
Enhancement of HIV transmission by hormones and bacterial metabolites
Role: PI

R01 HD077886-01 Tilton, John Christian (PI) 09/13/13-05/31/18
Enhancement of HIV transmission by hormones and bacterial metabolites
Role: PI

R01 HD077886-02 Tilton, John Christian (PI) 09/13/13-05/31/18
Enhancement of HIV transmission by hormones and bacterial metabolites
Role: PI

R01 HD077886-04 Tilton, John Christian (PI) 09/13/13-05/31/18
Enhancement of HIV transmission by hormones and bacterial metabolites

Role: PI

Completed Research Support

R21 AI113148-02 Tilton, John Christian (PI) 07/01/14-06/30/16
Detection of Latent HIV Infection Using Selective Reaction Monitoring Mass Spectr
Role: PI

R21 AI113148-01 Tilton, John Christian (PI) 07/01/14-06/30/16
Detection of Latent HIV Infection Using Selective Reaction Monitoring Mass Spectr
Role: PI

F32 AI077370-01 Tilton, John Christian (PI) 02/01/08-01/31/11
Mechanisms of HIV Resistance to CCR5 Inhibitors and Consequences for Pathogenesis
Role: PI

F32 AI077370-02 Tilton, John Christian (PI) 02/01/08-01/31/11
Mechanisms of HIV Resistance to CCR5 Inhibitors and Consequences for Pathogenesis
Role: PI

F32 AI077370-03 Tilton, John Christian (PI) 02/01/08-01/31/11
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