BIOGRAPHICAL SKETCH

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NAME	POSITION TITLE
Harding, Clifford V.	Professor and Chair
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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)*	MM/YY	FIELD OF STUDY
Harvard College, Cambridge, MA	AB	1975-1979	Biology
Washington University, St. Louis, MO	MD/PhD	1979-1985	Cell Biology
Washington Univ Sch. of Medicine, St. Louis, MO	Resident	1985-1989	Pathology/Immunology
Washington Univ Sch. of Medicine, St. Louis, MO	Chief Res.	1989-1990	Pathology/Immunology

A. Personal Statement:

Clifford V. Harding, MD, PhD, is Professor and Chair of Pathology at Case Western Reserve University. He also serves as Director of the CWRU Medical Scientist Training Program (MSTP). He has a long-standing productive NIH-funded research program on antigen presenting cells (APCs) and their regulation by Toll-like receptors (TLRs) or infection with *Mycobacterium tuberculosis* (Mtb) or HIV. He has over 170 publications on topics in immunology and infectious diseases. In recent years, a major focus has been regulation of APCs by TLR2 agonists expressed by Mtb (lipoproteins and glycolipids). Other projects focus on regulation of immune responses by TLR9 and type I interferon, as well as regulation of signaling by these receptors.

B. Positions and Honors:

1989-1990	Instructor in Pathology, Washington University School of Medicine, St. Louis, MO
1990-1993	Assistant Professor of Pathology, Washington University School of Medicine
1989-1993	Attending Physician, Barnes Hospital, St. Louis, MO
1993-1996	Assistant Professor of Pathology, Case Western Reserve Univ. School of Medicine
1993-present	Senior Staff Physician, University Hospitals of Cleveland Case Medical Center
1996-1999	Associate Professor of Pathology (primary) and Oncology (secondary), CWRU
1999-present	Professor of Pathology (primary) and Oncology (secondary), CWRU
2001-present	Director, CWRU Medical Scientist Training Program (MSTP)
2004-present	Adjunct Staff, Dept. of Immunology, Lerner Research Institute, Cleveland Clinic Foundation
2005-present	Director, CWRU Immunology Training Program
2006-present	Secondary appointment, CWRU Center for Clinical Investigation
2007-present	Director, CWRU Clinical and Translational Scientist Training Program (CTSTP)
2008-present	Chair, Department of Pathology, CWRU and UHC (Interim, 2008-2010)
2011-present	Secondary appointment, Division of Infectious Diseases and HIV Medicine

Honors:

1979	Magna cum laude with highest honors in Biology; Phi Beta Kappa (Harvard College)
1989	American Association of Pathologists Experimental Pathologist-in-Training Award
1991	Pfizer Scholar & American Cancer Society Junior Faculty Research Award
1996-2001	AITRC Study Section, NIH (Chair, 1999-2001)
1995-present	Reviewer for NIH study sections, American Cancer Society, Wellcome Trust, Netherlands Organization for Scientific Research (NWO), Dutch Cancer Society, Israel Science Foundation
1994-2001	Editorial Boards, Traffic, Cellular Microbiology, Advances in Anatomic Pathology
2006-present	Editorial Board, Biology Direct Immunology
2001-present	Member, Faculty of 1000
2002, 04, 05	Section Editor, Current Opinion in Immunology

2008- 2010 Midwest Regional Center of Excellence for Biodefense and Emerging Infectious Diseases Research (MRCE) Steering Committee

2009-present MD-PhD Section Steering Committee for American Association of Medical Colleges (AAMC) Group on Graduate Research, Education and Training (GREAT), July 2009-present.

2009-present American Association of Immunologists Committee on Public Affairs. July 2009-2012.

C. Publications (selected from over 170 publications):

1. Harding C, Heuser J & Stahl P. 1983. Receptor-mediated endocytosis of transferrin and recycling of the transferrin receptor in rat reticulocytes. J. Cell Biol. 97:329-339. (*first report of exosomes)
2. Harding, CV & Unanue ER. 1990. Quantitation of peptide-class II MHC complexes generated in antigen presenting cells and necessary for T cell stimulation. Nature 346:574-576.
3. Harding, CV, Collins, DS, Slot, JW, Geuze, HJ & Unanue ER. 1991. Liposome-encapsulated antigens are processed in lysosomes, recycled and presented to T cells. Cell 64:393-401.
4. Harding CV & Geuze HJ. 1992. Class II MHC molecules are present in macrophage lysosomes and phagolysosomes that function in the phagocytic processing of Listeria monocytogenes for presentation to T cells. J. Cell Biol. 119:531-542.
5. Pfeifer JD, Wick MJ, Roberts RL, Findlay KF, Normark SJ & Harding CV. 1993. Phagocytic processing of bacterial antigens for class I MHC presentation to T cells. Nature 361:359-362.
6. Harding CV & Geuze HJ. 1993. Immunogenic peptides bind to class II MHC molecules in an early lysosomal compartment. J. Immunol. 151:3988-3998.
7. Griffin J, Chu R & Harding CV. 1997. Early endosomes and a late endocytic compartment generate distinct species of peptide:MHC-II complexes via different mechanisms. J. Immunol. 158: 1523-1532.
8. Ramachandra L, Song R & Harding CV. 1999. Phagosomes are fully competent antigen processing organelles that mediate the formation of peptide:class II MHC complexes. J. Immunol. 162:3263-3272.
9. Noss EH, Pai RK, Sellati TJ, Radolf JD, Belisle J, Golenbock DT, Boom WH & Harding CV. 2001. Toll-like receptor 2-dependent inhibition of macrophage class II MHC expression and antigen processing by 19 kD lipoprotein of *Mycobacterium tuberculosis*. J. Immunol., 167: 910-918. PMID: 11441098
10. Sieg, S.F., Harding, C.V. and Lederman, M.M. 2001. HIV-1 infection impairs cell cycle progression of CD4(+) T cells without affecting early activation responses. J. Clin. Invest. 108: 757-764.
11. Ramachandra L, Noss EH, Boom WH & Harding CV. 2001. Processing of *Mycobacterium tuberculosis* antigen 85B involves intra-phagosomal formation of peptide:MHC-II complexes and is inhibited by live bacilli that decrease phagosome maturation. J. Exp. Med., 194:1421-1432.
12. Pai RK, Askew D, Boom WH & Harding CV. 2002. Regulation of class II MHC expression in APCs: Roles of types I, III and IV class II transactivator. J. Immunol. 169: 1326-1333.
13. Pai RK, Convery M, Hamilton TA, Boom WH & Harding CV. 2003. Inhibition of IFN-γ-induced class II transactivator expression by a 19-kDa lipoprotein from *Mycobacterium tuberculosis*: A potential mechanism for immune evasion. J Immunol 171: 175-184.
14. Pai RK, Pennini ME, Tobian AAR, Canaday DH, Boom WH & Harding CV. 2004. Prolonged Toll-like receptor signaling by *Mycobacterium tuberculosis* and its 19-kDa lipoprotein inhibits interferon-gamma-induced gene regulation in macrophages. Infect Immun 72:6603-6614.
15. Jiang, W, Lederman, MM, Salkowitz, JR, Harding, CV & Sieg, SS. 2005. CpG ODN induces monocyte maturation in cells from healthy individuals and HIV-infected patients. J. Virol. 79: 4109-4119.
16. Kuchtey, J, Chefalo, PJ, Ramachandra, L & Harding, CV. 2005. Enhancement of dendritic cell antigen cross presentation by CpG DNA involves type I IFN and stabilization of class I MHC mRNA. J Immunol 175: 2244-2251.
17. Pennini, ME, Pai, RK, Schultz, DC, Boom, WH & Harding, CV. 2006. *Mycobacterium tuberculosis* 19-kDa lipoprotein inhibits IFN-g-induced chromatin remodeling of *MHC2TA* by TLR2 and MAPK signaling. J. Immunol. 176: 4323-4330. PMID: 16547269
18. Rodriguez, B, Lederman, MM, Jiang, W, Bazdar, DA, Gàrate, K, Harding, CV & Sieg, SF. 2006. Interferon-α differentially rescues CD4+ and CD8+ T cells from apoptosis in HIV infection. AIDS 20:1379-1389.
19. Pecora, ND, Gehring, AJ, Canaday, DH, Boom, WH & Harding, CV. 2006. *M. tuberculosis* LprA is a lipoprotein agonist of TLR2 that regulates innate immunity and APC function. J. Immunol. 177:422-429.
20. Pennini, ME, Yang, J, Croniger, CM, Boom, WH and Harding, CV. 2007. C/EBP-beta binds to CIITA promoters and inhibits CIITA expression in response to M. tuberculosis 19-kDa lipoprotein. J. Immunol. 179: 6910–6918. PMC2631233.

21. Funderberg, N., Lederman, M.M., Feng, Z., Drage, M.G., Jadlowsky, J. Harding, C.V., Weinberg, A. and Sieg, S.F. 2008. Human beta-defensin-3 activates professional antigen-presenting cells via Toll-like receptors 1 and 2. Proc. Natl. Acad. Sci. USA 104: 18631-18635. PMCID:PMC2141828
22. Anis, M.M., Fulton, S.A., Reba, S.M., Liu, Y., Harding, C.V. and Boom, W.H. 2008. Modulation of pulmonary dendritic-cell function during mycobacterial infection. Infect. Immun 76: 671-677. PMCID:PMC2223454
23. Jiang, W, MM Lederman, RJ Mohner, B Rodriguez, TM Nedrich, CV Harding & SF Sieg. 2008. Impaired naive and memory B cell responsiveness to TLR9 stimulation in HIV-infection. *J Virol*. 82: 7837-7845. PMCID:PMC2519583
24. Drage, M.G., Pecora, N.D., Hise, A.G., Febbraio, M., Silverstein, R.L., Golenbock, D.T., Boom, W.H. and Harding, C.V. 2009. TLR2 and its co-receptors determine responses of macrophages and dendritic cells to lipoproteins of *Mycobacterium tuberculosis.* Cell. Immunol. 258: 29-37. PMCID:PMC2730726.
25. Pecora, N.D., Fulton, S.A., Reba, S.M., Drage, M.G., Simmons, D.P., Urankar-Nagy, N.J., Boom, W.H. and Harding, C.V. 2009. *Mycobacterium bovis* BCG decreases MHC-II expression *in vivo* on murine lung macrophages and dendritic cells during aerosol infection. Cell. Immunol. 254: 94-104. PMCID:PMC2653222
26. Hardy, G.A., Sieg, S.F., Rodriguez, B., Jiang, W., Asaad, R., Lederman, M.M. and Harding, C.V. 2009. Desensitization to type I interferon in HIV-1 infection correlates with markers of immune activation and disease progression. Blood, 113: 5497-5505. PMCID:Pmc2689050.
27. Qu, Y., Ramachandra, L., Mohr, S., Franchi, L., Harding, C.V., Nunez, G. and Dubyak, G.R. 2009. P2X7 receptor-stimulated secreation of MHC-II-containing exosomes requires the ASC/NLRP3 inflammasome but is independent of caspase-1. 2008. J. Immunol. 182: 5052-5062. PMC2768485.
28. Mahon, R.N., Rojas, R.E., Fulton, S.A., Franko, J., Harding, C.V.# and Boom, W.H.# 2009. *Mycobacterium tuberculosis* cell wall glycolipids directly inhibit CD4+ T cell activation by interfering with proximal TCR signaling. Infect. Immun. 77: 4574-4583. #Joint senior authors. PMCID:PMC2747961.
29. Liu, Y, Gray, RC, Hardy, GAD, Kuchtey, J, Abbott, DW, Emancipator, SN and Harding, CV. 2010. CpG-B oligodeoxynucleotides inhibit Toll-like receptor-dependent and independent induction of type I IFN in dendritic cells. J. Immunol. 184:3367-3376. PMCID: PMC2892962.
30. Simmons, D.P., Canaday, D.H., Liu, Y., Li, Q., Huang, A., Boom, W.H. and Harding, C.V. 2010. *Mycobacterium tuberculosis* and TLR2 agonists inhibit induction of type I IFN and MHC-I antigen cross processing by TLR9. J. Immunol. 185: 2405-2415. PMCID: PMC2990778.
31. Reuter, M.A., Pecora, N.D., Harding, C.V., Canaday, D.H., McDonald, D. 2010. *Mycobacterium tuberculosis* promotes HIV trans-infection and suppresses major histocompatibility complex class II antigen processing by dendritic cells. J. Virol. 84: 8549-8560. PMCID: PMC2919047.
32. Harding, C.V. and Boom, W.H. 2010. Regulation of antigen processing by *Mycobacterium tuberculosis*: a role for Toll-like receptors. Nature Rev Microbiol. 8: 296-307. NIHMSID269226.
33. Drage, M.G., Tsai, H.-C., Pecora, N.D., Cheng, T.-Y., Arida, A.R., Shukla, S., Rojas, R.E., Moody, D.B., Boom, W.H., Sacchettini, J.C., and Harding, C.V. 2010. *Mycobacterium tuberculosis* lipoprotein LprG (Rv1411c) binds triacylated glycolipid agonists of Toll-like receptor 2. Nature Struct Mol Biol. 17: 1088-1095. PMCID: PMC2933325.
34. Ramachandra, L., Qu, Y., Wang, Y., Cobb, B., Takatsu, K., Boom, W.H., Dubyak, G.R. and Harding, C.V. 2010. *Mycobacterium tuberculosis* synergizes with ATP to induce release of microvesicles and exosomes containing MHC-II molecules capable of antigen presentation. Infect Immun. 78:5116-5125. PMC2981298.
35. Jiang, W., Lederman, M.M., Harding, C.V. and Sieg, S.F. 2011. Presentation of soluble antigens to CD8+ T cells by CpG ODN-primed human naïve B cells. J. Immunol., In press. NIHMS265059.
36. Lancioni C. L., Li Q., Thomas J. J., Ding X., Thiel, D., Drage M. G., Pecora N. D., Ziady A. G., Shank S. L., Harding C.V., **Boom W. H**. and Rojas R. E. 2011. *Mycobacterium tuberculosis* lipoproteins directly regulate human memory CD4+ T cell activation via TLR2/1. Infect Immun, 79:663-73, 2011. PMC3028837.
37. Liu, Y.C., Simmons, D.P., Li, X., Abbott, D., Boom, W.H., Harding, C.V. 2012. TLR2 signaling depletes IRAK1 and inhibits induction of type I IFN by TLR7/9. Submitted.
38. Simmons, D.P., Canaday, D.H., Meyerson, H.J., Liu, Y.C., Wang, Y., Boom, W.H. and Harding, C.V. 2012. Type I interferon drives a distinctive dendritic cell maturation phenotype that allows continued class II MHC synthesis and antigen processing. Submitted.

D. Current Research Support:

NIH R01 AI035726 (Harding, PI). Period: 05/01/1994-12/31/2011
Class II MHC Transport and Function
Goals: 1. Characterize immune regulation by MTB lipoproteins. 2. Dissect molecular mechanisms whereby prolonged PAMP exposure inhibits macrophage MHC-II APC function. 3. Study APC modulation in vivo.

NIH R01 AI034343 (Harding, PI). Period: 09/01/1994 - 05/31/2013
Bacterial and Liposomal Antigen Processing
Goals: To investigate class I MHC processing of particulate and bacterial antigens, including *Mycobacterium tuberculosis* for MHC-I presentation to CD8 T cells. Aim 1: Mechanisms of cross-processing of MTB. Aim 2: Study lung APC antigen cross processing function. Aim 3: Define regulation of cross processing by MTB, TLRs and type I IFN.

NIH R01 R01 AI069085 (Harding, PI). Period: 12/01/2006-11/30/2012
M. tuberculosis lipoprotein-TLR2 interactions
Aims: Determine receptor dependence (e.g.TLR1/2/6, CD14, CD36) of recombinant MTB lipoproteins. Construct recombinant TLR2, TLR1 and TLR6 for direct binding assays with recombinant lipoproteins to define structural requirements for ligand binding to TLR2.

NIH R01 AI027243 (Boom, PI; Harding, Co-Investigator). Period: 02/01/1989 – 06/30/2012
Heterogeneity of T-Cells in *M. tuberculosis* Infection
Goals: 1. Study regulatory roles of cytokines (IFN-g, IL-10, TGF-b) and mycobacterial constituents for CD4+ T cell responses. 2. Study CD8+ T cell responses to MTB with focus on 44 kDa Rv0341 and 71 kDa Rv3808c proteins as Ags. 3. Study gamma-delta T cell activation by phosphoantigens, modulation of presentation to gamma-delta T cells by cytokines; study mechanism of gamma-delta T cell-mediated MTB growth inhibition.

P01 AI076174 (Lederman, PI; Harding, Co-Investigator) Period: 08/01/08-07/31/13
Defining the Pathogenesis of Immune Deficiency in Chronic HIV Infection
The Cleveland Immunopathogenesis Consortium (CLIC), including investigators at 10 academic and research institutions in the United States and Canada, will study mechanisms whereby HIV infection results in progressive immune deficiency. Project 1: Bystander activation drives T cell losses in chronic HIV infection (Lederman). Project 2: Loss of intestinal barrier function in HIV infection (Levine).
Role, Harding: Co-Investigator in Projects 1 and 2.

Training Grants:

NIH T32 GM07250 (Harding, PI). Period: 07/01/1975-06/30/2014
"Medical Scientist Training Program"
Goal: Training of MD/PhD students for successful careers in biomedical research.

NIH UL1 RR024989 (Davis) and TL1 RR024991 (Davis; PI of CTSA; Harding, Director of TL1 component).
Period: 09/17/2007-05/31/2012
“Case Western Reserve University/Cleveland Clinic CTSA” TL1 component
Goal: Training in clinical and translational research.

NIH T32 AI089474 (Harding)
Period: 07/01/2010-06/30/2015
“Immunology Training Program – Predoctoral”
Goal: PhD training in immunology and related fields via the Immunology Training Program.