BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Christina Hirsch	POSITION TITLE
eRA COMMONS USER NAME (credential, e.g., agency login) CHIRSCH	Associate Professor of Medicine

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Christian Albrecht University, Kiel, Germany		1983	Medicine
Julius Maximilian University, Sanderring	M.D.	1987	Medicine
Julius Maximilian University, Sanderring	Ph.D.	1988	Medicine/Immunology

A. Positions and Honors

1988-89 Intern in Internal Medicine, Meridia Huron Hospital, Cleveland, Ohio
1989-91 Resident in Internal Medicine, Metro Health Med. Center, Cleveland, Ohio
1991-94 Fellow in Pulmonary and Critical Care Medicine, Case Western Reserve University and MetroHealth Medical Center Combined Fellowship Program, Cleveland, Ohio
1994-96 Postdoctoral Research Fellow (Laboratory of JJ Ellner), Division of Infectious Diseases, Case Western Reserve University, Cleveland, Ohio
1996-1999 Instructor, Division of Infectious Diseases, Case Western Reserve University, Cleveland, Ohio
1999-2005 Assistant Professor of Medicine, Division of Infectious Diseases, Case Western Reserve University
2005-pres. Associate Professor of Medicine, Division of Infectious Diseases, Case Western Reserve University

Other Experience and Professional Memberships

American College of Physicians
American College of Chest Physicians
American Thoracic Society
American Medical Association

B. Selected peer-reviewed publications (in chronological order)

1. Hirsch CS, Ellner JJ, and Rich EA: Complement receptor-mediated uptake and tumor necrosis factor alpha-mediated growth inhibition of *Mycobacterium tuberculosis* by human alveolar macrophages. J Immunol 152:743, 1994.
2. Hirsch CS, Yoneda T, Averill L, Ellner JJ, and Toossi Z. Enhancement of intracellular growth of *Mycobacterium tuberculosis* in human monocytes by transforming growth factor β J Inf Dis 170:1229, 1994.
3. Toossi Z, Hirsch CS, Hamilton BD, Knuth CK, Friedlander MA, and Rich EA. Decreased production of transforming growth factor β1 (TGF-β1) in human alveolar macrophages. J Immunol 156:3461, 1996.
4. Hirsch CS, Hussain R, Toossi Z, Dawood G, Shahid F, and Ellner JJ. Crossmodulation by transforming growth factor β in human tuberculosis; Suppression of antigen-driven blastogenesis and interferon γ production. Proc Natl Acad Sci USA 93:3193, 1996.
5. Hirsch CS, Ellner JJ, Blinkhorn R, and Toossi Z. Immune enhancing effects of natural inhibitors of TGF-β; increases in T - cell responses in TB patients and inhibition of intracellular growth of MTB. Proc Natl Acad Sci USA 94:3926,1997.
6. Toossi Z, Mincek M, Seeholtzer E, Fulton SA, Hamilton BD, and Hirsch CS. Modulation of IL-12 by transforming growth factor - β (TGF-β) in *Mycobacterium tuberculosis* infected mononuclear phagocytes and in patients with active tuberculosis. J Clin Lab Immunol 49:59-75, 1997.

7. Hirsch CS, Toossi Z, Vanham G, Johnson JL, Peters P, Okwera A, Mugerwa R, Mugeyenyi P, and Ellner JJ. Apoptosis and T-cell hyporesponsiveness in pulmonary tuberculosis. J Inf Dis 179:945-53, 1999.
8. Wilkinson RJ, Patel P, Llewellyn M, Hirsch CS, Pasvol G, and Toossi Z. The influence of polymorphism within the Interleukin 1 receptor antagonist gene on disease expression, delayed type hypersensitivity, and cytokine production in human tuberculosis. J Exp Med 189:1863-1873, 1999.
9. Hirsch CS, Toossi Z, Othieno C, Johnson JL, Schwander S, Robertson S, Wallis RS, Okwera A, Mugerwa R, Edmonds K, Peters P, and Ellner JJ. Depressed T-cell IFN-γ responses in pulmonary tuberculosis: Analysis of underlying mechanisms and modulation with therapy. J Inf Dis 180:2069-73, 1999.
10. Othieno C, Hirsch CS, Hamilton BD, Wilkinson K, Ellner JJ, and Toossi Z. Interactions of MTB-induced TGF-β and IL-10. Infect Immun 67:5730-5, 1999.
11. Johnson JL, Kamya MR, Okwera A, Loughlin AM, Nyole S, Hom DL, Wallis RS, Hirsch CS, Wolski K, Foulds J, Mugerwa RD, and Ellner JJ. A controlled trial of heat-killed Mycobacterium vaccae as a therapeutic vaccine in HIV-non-infected Ugandans with pulmonary tuberculosis: Microbiologic, radiographic and immunologic activity. J Infect Dis 181:1304-12, 2000.
12. Ellner JJ, Hirsch CS, and Whalen CW. Correlates of protective immunity to Mycobacterium tuberculosis in humans. Clin Inf Dis, 30: S279-S282, 2000.
13. Hertoghe T, Wajja A, Ntambi E, Okwera A, Abdel Aziz M, Hirsch CS, Johnson JL, Mugerwa R, Mugeyenyi P, Colebunders R, Thielemans K, Ellner JJ, and Vanham G. T-cell activation, apoptosis and regulatory cytokine production in the co-pathogenesis of HIV and pulmonary tuberculosis. Clin Exper Immunol, 122: 350-7, 2000.
14. Hirsch CS, Toossi Z, Johnson JL, Luzze H, Ntambi E, Peters P, McHugh M, Okwera A, Joloba M, Mugeyenyi P, Mugerwa RD, Terebuh P, and Ellner JJ. Augmentation of apoptosis and IFN-γ production at sites of active MTB infection in human tuberculosis. J Infect Dis,183: 779-88, 2001.
15. Toossi Z, Mayanja-Kizza H, Hirsch CS, Edmonds KL, Spahlinger T, Hom DL, Aung H, Mugeyenyi P, Ellner JJ, and Whalen CW. Impact of tuberculosis on Human Immunodeficiency Virus-1 (HIV-1) activity in dually infected patients. Clin Exper Immunol, 123: 233-8, 2001.
16. Mayanja-Kizza H, Waija A, Wu M, Ssengoba A, Peters P, Nalugwa G, Mubiru F, Nassali A, Aung H, Herthoge T, Vanham G, Hirsch CS, Whalen CW, Ellner JJ, and Toossi Z. Activation of Beta-chemokines and CCR-5 and enhanced HIV-1 activity in HIV-infected patients with tuberculosis. J Infect Dis, 183: 1801-4, 2001.
17. Mayanja-Kizza H, Johnson JL, Hirsch CS, Peters P, Surewicz K, Wu M, Nalugwa G, Mubiru F, Luzze H, Waija A, Aung H, Ellner JJ, Whalen CW, and Toossi Z. Macrophage activating cytokines in HIV-1 infected and uninfected subjects with pulmonary tuberculosis. J Infect Dis, 183: 1805-9, 2001.
18. Luzze H, Elliot AM, Joloba ML, Odida ML, Oweka-Onyee J, Nakiyingi J, Quigley M, Hirsch CS, Mugerwa RD, Okwera A, and Johnson JL. Evaluation of suspected tuberculous pleurisy: Clinical and diagnostic findings in HIV-1-positive and HIV-negative adults in Uganda. Int J Tuberc Lung Dis, 5: 746-53, 2001.
19. Toossi Z, Johnson JL, Kanost AR, Wu M, Luzze H, Peters P, Okwera A, Joloba M, Mugeyenyi P, Mugerwa RD, Terebuh P, Aung H, and Hirsch CS. Increased replication of Human Immunodeficiency Virus-1 (HIV-1) at sites of active M. tuberculosis infection: Potential mechanisms of viral activation. J AIDS. 184:1127-33, 2001.
20. Lawn SD, Pisell T, Hirsch CS, Butera ST, Toossi Z. Anatomic and cellular compartments of virus replication in persons with tuberculosis and human immunodeficiency virus type 1 coinfection. J Infect Dis, 184:1127-33, 2001.
21. Hirsch CS, and Johnson JL. Preventive Therapy against tuberculosis – New U.S. guidelines. Infect Dis Clin Pract, 10:93-100, 2001.
22. Collins KR, Quiñones-Mateu M, Wu M, Luzze H, Johnson JL, Hirsch C, Toossi Z, Arts EJ. Human Immunodeficiency virus type 1(HIV-1) quasispecies at the sites of Mycobacterium tuberculosis infection contribute to systemic HIV-1 heterogeneity.J Virol, 76:1697-1706, 2002.
23. Ribeiro-Rodrigues R, Resende Co T, Ribeiro F, Palaci M, Johnson JL, Sá RT, Maciel EL, Pereira Lima FL, Dettoni V, Toossi Z, Boom WH, Dietze R, Ellner JJ, and Hirsch CS. Sputum cytokine levels in patients with pulmonary tuberculosis as markers of response to treatment. Clin Diag Lab Immunol, 9:818-823, 2002.
24. Hoft DF, Worku S, Kampmann B, Whalen CS, Ellner JJ, Hirsch CS, Brown RB, Larkin R, Li Q, Hyun J, and Silver RF. Investigation of the relationships between immune-mediated inhibition of mycobacterial

growth and other potential surrogate markers of protective TB immunity. J Infect Dis, 186:1448-57, 2002.
25. Johnson JL, and Hirsch CS. Aspiration Pneumonia – Recognizing and Managing a Potentially Growing Disorder. Postgrad Med,113 99-102, 105-106, 111-112, 2003.
26. Johnson JL, Ssekasanvu E, Okwera A, Mayanja H, Hirsch CS, Nakibali JG, Jankus DD, Eisenach KD, Boom WH, Ellner JJ, Mugerwa RD; Uganda-Case Western Reserve University Research Collaboration. Randomized trial of adjunctive interleukin-2 in adults with pulmonary tuberculosis. Am J Respir Crit Care Med, 168: 185-91, 2003.
27. Islam N, Kanost RA, Teixeira-Johnson L, Hejal R, Aung H, Wilkinson RJ, Hirsch CS, and Toossi Z. The role of cellular activation and tumor necrosis factorα (TNFα) in the early expression of *Mycobacterium tuberculosis* 85B mRNA in human alveolar macrophages. J Infect Dis, 190:341-51, 2004.
28. Toossi Z, Mayanja-Kizza H, Kanost A, Edmonds K, McHugh M, and Hirsch C. Protective responses inTuberculosis: Induction of genes for interferon gamma and cytotoxicity by Mycobacterium tuberculosis and during human tuberculosis. *Scand J Immunol*, 60:299-306, 2004.
29. Aung, H., Wu, M., Johnson, J. L., Hirsch, C. S. and Toossi, Z. Bioactivation of latent transforming growth factor beta1 by Mycobacterium tuberculosis in human mononuclear phagocytes Scand J Immunol **2005**.61, 558-65.
30. Hirsch, C. S., Johnson, J. L., Okwera, A., Kanost, R. A., Wu, M., Peters, P., Muhumuza, M., Mayanja-Kizza, H., Mugerwa, R. D., Mugyenyi, P., Ellner, J. J. and Toossi, Z. Mechanisms of apoptosis of T-cells in human tuberculosis J Clin Immunol **2005**.25, 353-64.
31. Toossi, Z., Mayanja-Kizza, H., Baseke, J., Peters, P., Wu, M., Abraha, A., Aung, H., Okwera, A., Hirsch, C. and Arts, E. Inhibition of human immunodeficiency virus-1 (HIV-1) by beta-chemokine analogues in mononuclear cells from HIV-1-infected patients with active tuberculosis Clin Exp Immunol **2005**.142, 327-32.
32. Ribeiro-Rodrigues, R., Resende Co, T., Rojas, R., Toossi, Z., Dietze, R., Boom, W. H., Maciel, E. and Hirsch, C. S. A role for CD4CD25 T cells in regulation of the immune response during human tuberculosis Clin Exp Immunol **2006**.144, 25-34.
33. Whalen CC, Chiunda A, Zalwango S, Nshuti L, Jones-Lopez E, Okwera A, Hirsch C, Peters P, Boom WH, Mugerwa RD. Immune correlates of acute Mycobacterium tuberculosis infection in household contacts in Kampala, Uganda. Am J Trop Med Hyg, **75:**55-61, **2006**.
34. Resende Co, T., Hirsch, C. S., Toossi, Z., Dietze, R. and Ribeiro-Rodrigues, R. Intestinal helminth co-infection has a negative impact on both anti-Mycobacterium tuberculosis immunity and clinical response to tuberculosis therapy Clin Exp Immunol **2007**.147, 45-52.
35. Toossi, Z., Mayanja-Kizza, H., Lawn, S. D., Hirsch, C. S., Lupo, L. D. and Butera, S. T. Dynamic variation in the cellular origin of HIV type 1 during treatment of tuberculosis in dually infected subjects AIDS Res Hum Retroviruses **2007**.23, 93-100.

C. Research Support

Ongoing Research Support:

AI-95383 - W. Henry Boom MD (PI) 4/1/06-3/31/13
NIAID
Tuberculosis Research and Prevention Unit
Role: Co-investigator

The purpose of this contract is to conduct coordinated multi-disciplinary investigations of host immunologic mechanisms to *M. tuberculosis* in order to identify and validate surrogate markers for clinical use. Potential markers (in blood and sputum samples) specific to MTB infection and useful in distinguishing it from exposure to or infection with BCG and atypical mycobacteria are currently being evaluated in the context of population-based studies in Uganda and Brazil. Assays currently under investigation include MTB-antigen-induced production of cytokines in whole blood, assessment of IFN-γ, TNF-α, IL-6 and IL-8 levels in sputum from patients with TB and healthy PPD positive control subjects, and killing of MTB in mononuclear phagocytes in vitro. Recently, the infrastructure for bronchoscopy and BAL of smear $\angle$negative TB patients has been

established at the TBRU Brazil site under Dr. Hirsch's direction, thus allowing assessment of cytokines levels and of anti-MTB immune responses in primary lung T-cells and mononuclear phagocytes.

RO1 (HL51636) Zahra Toossi (PI) 8/1/04-7/31/09
NHLBI
Impact of Tuberculosis on HIV Disease
Role: Co-Investigator

This grant investigates the impact of TB on immunologic and virologic ifactors on HIV-1 disease. Aims are to 1. Determine the basis for transcriptional activation of HIV by MTB in mononuclear phagocytes. 2. Assess the role of excess cytokines and chemokines in viral production and to determine whether mechanisms of transcriptional activation of HIV are operative at sites of active MTB infection in HIV/TB patients with pleural TB. 3. Determine whether release of HIV virions by macrophages are effectively abrogated by ARV therapy during HIV/TB, and whether there is an associated change in viral set point and viral heterogeneity, and a decrease in frequency of latently infected mononuclear cells in lymph nodes.

Previous Research:

Contract (039DT303) Hirsch (PI) 7/15/02-9/30/06
CDC
Prospective Evaluation of Immunological Surrogate Markers of Susceptibility to *M. tuberculosis* Infection
This protocol is an immunological study to identify surrogates of protective immune responses to *M. tuberculosis* infection. It is a substudy conducted in the context of an already ongoing larger prospective study of contact investigations in the United States. Specifically, the association between transmission of MTB infection and contact to a case with active TB and levels of MTB antigen-induced cytokines (IFN-γ, TNF-α and IL-10) in whole blood cultures will be evaluated in an epidemiologically well defined US population (both foreign-born and US-born individuals) who have (foreign born) or have not received BCG (US born)

KO8 (AI01514) Hirsch (PI) 7/1/98 to 6/30/02

NIAID

Role of T-cell Apoptosis in the Immunopathogenesis of TB

The long-term objective of this project is to assess the role of apoptosis in immune responses in the peripheral blood from patients with pulmonary TB. Specifically the project studies the role of T-cell apoptosis in the profound immediate and persistent suppression of production of IFN-γ by PBMC from patients with TB and attempts to identify the molecular mechanisms involved in spontaneous and M. tuberculosis-induced apoptosis and to examine the contribution of blood monocytes to this process. The hypothesis being evaluated is that T-cells from patients with TB undergo both spontaneous and antigen-induced apoptosis at increased rates, resulting in decreased production of the immunoprotective cytokine IFN-γ. Decreased production of IFN-γ, in turn, may contribute to ineffective anti-MTB immunity and allow persistence of active MTB infection.