

Honor & Awards

T32 Predoctoral Fellowship Recipient 2010-2013

Michael N Hart Cellular and Molecular Pathology Best Poster Award

Talks and Presentations

Harding J.S. A Role for Anti-VEGF Drugs in Tuberculosis Therapy. Michael N. Hart Research Day, Aug 21 2014

Harding J.S. Immunity and Mycobacterial Granulomas. Cellular and Molecular Training Program Recruitment March 2 2014

Harding J.S. The Role of VEGF in Mycobacterial Granulomas. Dr. Thomas Horvath laboratory at Yale, February 7 2014

Harding J.S. The Role of VEGF In Mycobacterial Granulomas. Pathology and Laboratory Medicine Seminar Series Oct 30, 2013

Harding J.S. Y. Chen, Z. Fabry, A. Nagy, M. Sandor. Blocking Vascular Endothelial Growth Factor Reduces Granulomatous Inflammation During Murine Mycobacterial Infection. AAI Annual meeting, Honolulu, HI, May 5 2013

Harding J.S. Y. Chen, B. Clarkson, M. Harris, D. Stewart, H. Schreiber, Z. Fabry, M. Sandor. The Role of CCR2 and CCR7 on Dendritic Cell Movement and Phenotype During Mycobacterial Infection. AAI Annual meeting, Honolulu, HI, May 5 2013

Harding J.S. Granuloma Transplantation: An Approach to Study Mycobacterium-Host Interactions. Cellular and Molecular Training Program Recruitment February 27 & March 5 2013

Harding J.S. Mycobacterial Disease. Course Lecture for Pathology 803: Pathogenesis of Major Human Diseases Oct 19 2012

Harding J.S. The Role of VEGF in Mycobacterial Granulomas. Cellular and Molecular Pathology Student Seminar Series, October 18, 2012

Harding, J.S. P. Hulseberg, H. Schreiber, C. Altamirano, M. Sandor. Novel Model of Mycobacterial Dissemination: Comparison of the Local and Systemic Requirements for Host Protection Factors. Michael N. Hart Pathology Research Day (winner of best poster 2012) Aug 2011-2012

Harding J.S. The Role of VEGF in Mycobacterial Granulomas. World TB Day Symposium March 22, 2012

Harding J.S. A Novel Model of Mycobacterial Dissemination. Cellular and Molecular Pathology Student Seminar Series February 3, 2011

Harding, J.S. P. Hulseberg, H. Schreiber, C. Altamirano, M. Sandor. Novel Model of Mycobacterial Dissemination: Comparison of the Local and Systemic Requirements for Host Protection Factors. Keystone Symposia. Tuberculosis: Immunology, Cell Biology and Novel Vaccination Strategies. Vancouver CA, January 17, 2011

Harding J.S. The Role of VEGF in the Immune Response to Mycobacterium. Cellular and Molecular Pathology Student Seminar Series March 18, 2010

Harding J.S. Modeling Mycobacterium Tuberculosis Dissemination from the Granuloma. Cellular and Molecular Pathology Student Seminar Series April 9, 2009



The University of Wisconsin - Madison

CMP

Cellular and Molecular Pathology

Jeffrey Harding

Program of the Thesis Defense Seminar for the
Degree of Doctor of Philosophy
in Cellular and Molecular Pathology

“Granuloma Dynamics during
mycobacterial infection”

Wednesday, April 27, 2014

3 p.m.

Room 7001A

Wisconsin Institutes for Medical
Research

Research conducted in the lab of
Dr. Matyas Sandor, PhD
Department of Pathology & Laboratory Medicine



Cellular and Molecular
Pathology Graduate Program

Joanne Thornton
3170-10K MFCB

1685 Highland Avenue
Madison, WI 53705

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Jeffrey Harding's

Granuloma Dynamics during mycobacterial infection

Jeffrey Harding

Under the supervision of

Professor Matyas Sandor, PhD

at the University of Wisconsin-Madison

The granuloma is a collection of innate and adaptive immune cells organized with a defined spatial arrangement and cellular composition. Granulomatous inflammation is the hallmark of many infectious and autoimmune diseases, and is an important part of both protection and pathology in diseases including tuberculosis, leprosy, schistosomiasis, histoplasmosis, sarcoidosis, and Crohn's, among others. During infection with *Mycobacterium tuberculosis* (Mtb), the granuloma is the space where the pathogen is either killed by host immunity or able to persist and enter latency. These sites are the ecosystems that define the host-pathogen relationship and so understanding this space is a critical part of a completed understanding of tuberculosis pathogenesis, as well as that of other granuloma-induced diseases.

Our work has focused on understanding the dynamics of the granuloma. Granuloma dynamism is a context of granuloma biology that includes many poorly understood phenomenon, yet is clearly a defining aspect of granuloma form and function. This dynamism includes the activity of anti-microbial leukocytes needed for bacterial killing, as well as the ways that cell traffic to and from the granuloma dictates adaptive immune priming, granuloma repopulation, and granuloma reformation.

In the work presented here we investigate granuloma dynamics during mycobacterial infection under a combination of specific contexts including: 1) How granuloma-produced factors regulate inflammation and immunity and 2) The relationship between the local granuloma and the peripheral immune environments. We describe the upregulation and unappreciated role of specific granuloma factors, like VEGF, in granuloma cell recruitment and show the therapeutic potential of

reducing pathological inflammation by reducing VEGF's activity. We show that VEGF also increases lymph node access to granuloma-contained antigen by inducing lymphangiogenesis. Finally, we show that infected dendritic cells emigrate from the granuloma and get arrested by mycobacterial-specific T-cells in situ. We also show that these sites of arrest serve as foci for new inflammatory recruitment and result in granulomatous spreading in infected tissue. Together, our work supports an understanding of tuberculosis pathogenesis and more broadly, the granuloma biology common among autoimmune and infectious granuloma-inducing diseases.

Publications

1. **Harding J.S.**, Rayasam A, Schriber H, Fabry Z, Sandor M. Mycobacterium-Infected Dendritic Cells Disseminate Granulomatous Inflammation. *Manuscript Submitted to Journal of Clinical Investigations*
2. **Harding J.S.**, Fabry Z, Sandor M. Lymphangiogenesis is induced by mycobacterial-induced granuloma monocytes via VEGFR3 and regulates mycobacterium-specific T-cell priming. *Manuscript under review at The American Journal of Pathology, Aug 2014*
3. **Harding, J.S.**, Chen Y, Michael I, Fabry Z, Nagy A, Sandor M. Blockade of VEGF alleviates granulomatous pathology. *Manuscript under review at Nature, Aug 2014*
4. **Harding J.S.**, Sandor M. Pathology vs. Protection in tuberculosis: How knowledge of molecular regulators of cell recruitment can reduce pathological inflammation (2014). *Manuscript under review at Mycobacterial Diseases, Aug 2014*
5. Harris, M.G., Hulseberg P, Changying L, Karman J, Clarkson BD, **Harding J.S.**, Zhang M, Sandor A, Christensen K, Nagy A, Sandor M, Fabry Z. et al. Immune privilege of the CNS is not the consequence of limited antigen sampling. *Sci. Rep.* 4(2014).
6. **Harding, J.S.**, Schreiber, H.A. & Sandor, M. Granuloma transplantation: an approach to study mycobacterium-host interactions. *Front Microbiol* 2, 245 (2011). PMID: PMC3235768
7. Schreiber HA, **Harding J.S.**, Altamirano CJ, Hunt O, Huseberg PD, Fabry Z, Sandor M. Continuous Repopulation of Lymphocyte Subsets in Transplanted Mycobacterial Granulomas. *Eur J Microbiol Immunol (Bp)* 1, 59-69, doi:10.1556/EuJMI.1.2011.1.8 (2011). PMID: PMC3215294. December 2010
8. Schreiber HA, **Harding J.S.**, Hunt O, Altamirano CJ, Huseberg PD, Stewart D, Fabry Z, Sandor M. Inflammatory dendritic cells migrate in and out of transplanted chronic mycobacterial granulomas in mice. *J Clin Invest* 121, 3902-3913, doi:45113 [pii] 10.1172/JCI45113 (2011). PMID: PMC3195456
9. Schreiber HA, Hulseberg PD, Lee JE, Prechl J, Barta P, Szlavik N, **Harding J.S.**, Fabry Z, Sandor M. Dendritic Cells In Chronic Mycobacterial Granulomas Restrict Local Anti-bacterial T cell Response In a Murine Model. *PLoS One* 5, e11453, doi:10.1371/journal.pone.0011453 (2010). PMID: PMC2897891