Joseph N Blattman, Ph.D.

Assistant Professor, Arizona State University
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Education

Post-doctoral, Dept. of Immunology, University of Washington, Seattle, WA 2001-2005
Advisor Dr. Philip D. Greenberg
Ph.D., Immunology and Molecular Pathogenesis, Emory University, Atlanta, GA 2001
Advisor Dr. Rafi Ahmed
B.S. *with Distinction,* Biochemistry, University of Nevada, Reno, NV 1996
Advisor Dr. Stephen C. St Jeor

Professional

Assistant Professor, School of Life Sciences, Center for Infectious Diseases and Vaccinology, Arizona State University, Tempe, AZ 2011-current
Affiliate Investigator, Vaccine and Infectious Disease Institute Fred Hutchinson Cancer Research Center, Seattle, WA 2010-2011
Research Affiliate, Washington National Primate Research Center Seattle, WA 2008-2011
Affiliate Investigator, Program in Immunology, Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA 2007-2011
Research Assistant Professor, Department of Immunology, University of Washington, Seattle, WA 2006-2011
Research Associate,Program in Immunology, Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA 2005-2007
Laboratory Director, Cellular Immunology Core Laboratory, Washington National Primate Research Center, University of Washington, Seattle, WA 2005-2007
Acting Instructor, Department of Immunology, School of Medicine, University of Washington, Seattle, WA 2005-2006

Awards

Arizona State University, School of Life Sciences Startup Award 2011
Center for AIDS Research Award Recipient 2009-2011
Bill & Melinda Gates Foundation Grant Recipient 2006-2011
NIH Howard Temin Career Development Award (K01) Recipient 2006-2011
NIH Clinical Research Loan Repayment Program Recipient 2004-2007
AAAS/Science Program for Excellence in Science 2004
Cancer Research Institute/James E. Siegel Perpetual Fellowship Award 2002-2005
American Cancer Society Post-Doctoral Fellowship, (awarded, *not accepted*) 2002
UW Immunology Department Training Grant Fellowship (awarded, *not accepted*) 2002

Publications

1. Zajac A.J., K. Murali-Krishna, **J.N. Blattman,** and R. Ahmed. (1998) Therapeutic Vaccination Against Chronic Viral Infection: The Importance of Cooperation Between $CD4^+$ and $CD8^+$ T Cells, *Curr. Opin. Immunol*. **10**(4):444-449.
2. Zajac A.J., **J.N. Blattman**, K. Murali-Krishna, D.J.D. Sourdive, M. Suresh, J.D. Altman, and R. Ahmed. (1998) Viral Immune Evasion due to Persistence of Activated T Cells Without Effector Function, *J. Exp. Med*. **188**(12):2205-2213.
3. **Blattman J.N.***, A.J. Zajac*, K. Murali-Krishna, D.J.D. Sourdive, M. Suresh, J.D. Altman, and R. Ahmed. (1999) T Cell Anergy During Chronic Viral Infection *in* "Factors in the

Emergence and Control of Rodent-borne Diseases (Hantaviral and Arenal Diseases)", J.F. Saluzzo and B. Dodet, ed., Elsevier, Paris, pp. 243-253.
4. **Blattman J.N.**, D.J.D. Sourdive, K. Murali-Krishna, R. Ahmed, and J.D. Altman. (2000) Evolution of the T Cell Repertoire during Primary, Memory, and Recall Responses to Viral Infection, *J. Immunol.*, **165**(11):6081-6090.
5. **Blattman J.N.**, R. Antia, D.J.D. Sourdive, K. Murali-Krishna, X. Wang, S.M. Kaech, J.D. Altman, and R. Ahmed. (2002) Estimating the Precursor Frequency of Naïve Antigen-Specific $CD8^+$ T Cells, *Brief Definitive Report, J. Exp. Med.* **195**(5):657-664.
6. **Blattman J.N.**, L.E. Cheng and P.D. Greenberg. (2002) CD8+ T cell responses: It's all downhill after their prime…, *Nat. Imm.* **3**(7):601-602.
7. Slifka M.K., **J.N. Blattman**, D.J.D. Sourdive, F. Liu, D.L. Huffman, T. Wolfe, A. Hughes, M.B.A. Oldstone, R. Ahmed and M.G. von Herrath. (2003) Preferential Escape of Subdominant $CD8^+$ T cells during Negative Selection Results in an Altered Antiviral T cell Hierarchy, *J. Immunol.* **170**(3):1231-1239.
8. Seiffert M., J.M. Custodio, I. Wolf, M. Harkey, Y. Liu, **J.N. Blattman**, P.D. Greenberg and L.R. Rohrscneider. (2003) Gab3-Deficient Mice Exhibit Normal Development and Hematopoiesis and are Immunocompetent, *Mol. Cell. Biol.* **23**(7):2415-2424.
9. Wherry E.J., **J.N. Blattman**, K. Murali-Krishna R.G. van der Most and R. Ahmed. (2003) Viral Persistence Alters CD8 T-cell Immunodominance and Tissue Distribution and Results in Distinct Stages of Functional Impairment, *J. Virol.* **77**(8):4911-4927.
10. **Blattman J.N.**, J.M. Grayson, E.J. Wherry, S.M. Kaech, K.A. Smith and R. Ahmed. (2003) Therapeutic Use of IL-2 to Enhance Antiviral T-cell Responses *In Vivo*, *Nat. Med.* **9**(5):540-547.
11. Ho W.Y., **J.N. Blattman**, M. Dossett, C. Yee and P.D. Greenberg. (2003) Adoptive Immunotherapy: Engineering T Cell Responses as Biologic Weapons for Tumor Mass Destruction, *Cancer Cell* **3**(5):431-437.
12. Topp M., S. Riddell, Y. Akatsuka, M.C. Jensen, **J.N. Blattman** and P.D. Greenberg. (2003) Restoration of CD28 Expression in CD28-CD8+ Memory Effector T-cells Reconstitutes Antigen-Induced IL-2 Production, *Brief Definitive Report, J. Exp. Med.* **198**(6):947-955.
13. van der Most R.G., K. Murali-Krishna, J.G. Lanier, E.J. Wherry, M.T. Puglielli, **J.N. Blattman**, A.J. Zajac, A.D. Sette and R. Ahmed. (2003) Changing Immunodominance Patterns in Antiviral CD8 T cell Responses after Loss of Epitope Presentation or Chronic Antigen Stimulation, *Virology* **315**(1):93-102.
14. **Blattman J.N.** and P.D. Greenberg. (2004) Cancer Immunotherapy: A Treatment for the Masses, *Science* **305**(5681):200-205.
15. Zhang Y., **J.N. Blattman,** N.J. Kennedy, J. Duong, T. Nguyen, Y. Wang, R.J. Davis, P.D. Greenberg, R.A. Flavell and C. Dong. (2004) Regulation of Innate and Adaptive Immune Responses by MAP Kinase Phosphatase 5, *Nature* **430**(7001):793-797.
16. Wherry E.J., D.L. Barber, S.M. Kaech, **J.N. Blattman** and R. Ahmed. (2004) Antigen-Independent Memory CD8 T Cells do not Develop during Chronic Viral Infection, *Proc. Nat. Acad. Sci. USA* **101**(45):16004-16009.
17. Wherry, E.J., **J.N. Blattman**, and R. Ahmed. (2005) Low CD8 T-cell Proliferative Potential and High Viral Load Limit the Effectiveness of Therapeutic Vaccination, *J. Virol.* **79**(14):8960-8968.
18. **Blattman, J.N.** & P.D. Greenberg. (2006) PD-1 Blockade: Rescue From a Near-Death Experience, *Nat. Immunol.* 7(3):227-228.
19. Shin H., S. Blackburn, **J.N. Blattman**, & E.J. Wherry. (2007) Viral Antigen and Extensive Division Maintain Virus-Specific CD8 T Cells During Chronic Infection, *J. Exp. Med*. **204**(4):941-949.

20. Wherry E.J., S.J. Ha, S.M. Kaech, W.N. Haining, S. Sarkar, V. Kalia, S. Subramaniam, **J.N. Blattman**, D.L. Barber & R. Ahmed. (2007) Molecular Signature of $CD8^+$ T Cell Exhaustion during Chronic Viral Infection, *Immunity* **27**(4):670-684.
21. **Blattman J.N.**, E.J. Wherry, S.J. Ha, R.G. van der Most and R. Ahmed. (2009) The Impact of Epitope Escape on PD-1 Expression and CD8 T Cell Exhaustion During Chronic Infection, *J. Virol.* **83**(9):4386-4394.
22. Fowler C.C., L. Pao, **J.N. Blattman**, & P.D. Greenberg. (2010) SHP-1 in T Cells Limits the Production of CD8 Effector Cells Without Impacting the Formation of Long-lived Central Memory Cells, *J. Immunol.* 185(6):3256-3267.
23. **Blattman J.N.***, I.M. Stromnes*, X. Tan, S. Jeevanjee, H. Gu, & P.D. Greenberg. (2010) Abrogating Cbl-b- in Effector CD8(+) T Cells Improves the Efficacy of Adoptive Therapy of Leukemia in Mice, *J. Clin. Inv.* **120**(10):3722-3734.
24. Rhee E.G., **J.N. Blattman**, S.P. Kasturi, R.P. Kelley, D.R. Kaufman, D.M. Lynch, A. LaPorte, N.L. Simmons, S.L. Clark, B. Pulendran, P.D. Greenberg, & D.H. Barouch, (2011) Multiple Redundant Innate Immune Pathways Contribute to the Immunogenicity of Recombinant Adenoviral Vectors, *J. Virol.* **85**(1):315-323.
25. Johnson P.L.F., B.F. Kochin, M.S. McAfee, I.M. Stromnes, R.R. Regoes, R. Ahmed, **J.N. Blattman**, & R. Antia, (2011) Vaccination Alters the Balance between Protective Immunity, Exhaustion, and Pathology Following Disseminated Viremia, *J. Virol.* **85**(11):5565--5570.
26. Tan X., J.L. Sande, J.S. Pufnock, P.D. Greenberg** & **J.N. Blattman****. Use of Retinoic Acid as an Adjuvant to Imprint Mucosal Homing Properties to Vaccine-Induced T Cells, *J. Virol.* **85**(16):8316-8327.

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27. Scheitinger A.S., X. Tan, **J.N. Blattman**, and P.D. Greenberg. (2011) Epigenetic Memory Prevents Long-Term Rescue of Tolerant, Self-Reactive CD8 T cells, *Science* (*in press*).

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28. Stromnes, I.M., C.C. Fowler, **J.N. Blattman**, C. Georgopolos, M.S. McAfee, X. Tan, & P.D. Greenberg, Conditional Loss of SHP-1 in Tumor-Specific T Cells Improves Efficacy of Adoptive Immunotherapy of Cancer by Enhancing the Short-Term Accumulation of Effectors Cells *In Vivo*, *J. Immunol.* (*submitted*).
29. **Blattman J.N.,** I.M. Stromnes, E.J. Wherry, D. Liggitt, K.A. Smith, R. Ahmed, and P.D. Greenberg. IL-2-Induced TNF-Mediated Systemic Pathology and Vascular Leakage during Viral Infection is Mediated by CD8 T cells, *J. Exp. Med.* (*submitted*).
30. Stromnes I.M., S. JeevanJee, H. Gu, P.D. Greenberg and **J.N. Blattman,** Systemic Pathology in Cbl-b-deficient Mice is due to CD4 T Cell Production of IL-2 Acting on CD8 T cells, *J. Virol.* (*submitted*).
31. Wegmann F., N. Sheppard, S. Brinckmann, A.M. Harandi, K. Gartlan, W-L. Kok, L-P. Ho, E. Scherer, **J.N. Blattman**, G. Krashias, S.C. Eisenbarth, P.D. Greenberg, R. Flavell, J. Skehel, A. Moghaddam, and Q.J. Sattentau, Polyethyleneimine: A Potent and Modulatable Mucosal Adjuvant, *Nat. Biotech.* (*submitted*).

Invited Presentations

1. IL-2 Therapy During Viral Infection, CIS Symposium: Immunity to Latent/Chronic Viral Infections, K.A. Smith: Chair, Immunology 2000, AAI/CIS Joint Annual National Meeting, Seattle, WA, 14 May 2000.
2. Ignorance Exhaustion and Death; T Cell Fate and Function During Chronic Viral Infection, Program in Molecular and Cell Biology, School of Medicine, University of Nevada, Reno, NV, 19 Sept 2005.

3. Use of Humanized Mouse Models to Evaluate and Improve the Immunogenicity of Candidate HIV Vaccines, Grand Challenges in Global Health, Grand Challenge 4: Devise Reliable Testing Systems for New Vaccines, Washington D.C., 7 Oct 2006.
4. A Quantitative Mouse Model to Evaluate and Improve the Immunogenicity of Candidate HIV Vaccines, Fred Hutchinson Cancer Research Center, Vaccine & Infectious Diseases Institute Inaugural Symposia, Seattle, WA, 16 July 2007.
5. Validation of a Mouse Model for Assessing the Magnitude and Distribution of CD4 and CD8 T-Cell Responses to Multiple Candidate Vaccine Vectors, Collaboration for AIDS Vaccine Discovery Annual Meeting, Lausanne, Switzerland, 5 Dec 2007.
6. Use of TLR9 "Humanized" Mouse Models to Evaluate Immunogenicity of DNA Vaccines, Fred Hutchinson Cancer Research Center, Vaccine & Infectious Diseases Institute, Seattle, WA, 16 July 2008.
7. DNA Immunization: Surprisingly Efficient Induction of Mucosal T Cell Responses Occurs Independent of TLR9 Signals, Emory Vaccine Center, Emory University, Atlanta, GA, 14 Nov 2008.
8. DNA Immunization: Surprisingly Efficient Induction of Mucosal T Cell Responses Occurs Independent of TLR9 Signals, Collaboration for AIDS Vaccine Discovery Annual Meeting, Seattle, WA, 3 Dec 2008.
9. Comparison of the Immunogenicity of Adeno-Associated Viral Vectors Expressing Antigen-Flagellin Fusion Proteins, Collaboration for AIDS Vaccine Discovery Annual Meeting, Seattle, WA, 3 Dec 2008.
10. Abrogating Cbl-b in Antigen-Specific Effector CD8 T Cells Improves Ant-Viral Immune Responses and Adoptive Therapy of Disseminated Leukemia, Fred Hutchinson Cancer Research Center, Vaccine & Infectious Diseases Institute, Seattle, WA, 9 Oct 2009.
11. Development of HIV-specific TCR-transgenic Mouse Models, AIDS Vaccine 2009, Paris, France, 22 Oct 2009.
12. Epitope Immunodominance of T Cell Responses is Dictated by Priming Hierarchy, King's College, London, England, 26 Oct 2009.
13. Development of TCR-Transgenic Mouse Models for Evaluating Vaccine-Induced T Cell Immunity, Collaboration for AIDS Vaccine Discovery Annual Meeting, Miami, FL, 2 Dec 2009.
14. The Problem with Persistent Viral Infections, Workshop on the Immunological Basis of Vaccine Efficacy, Vaccine and Infectious Disease Institute, Fred Hutchinson Cancer Research Center, Seattle, WA, 14 Dec 2009.
15. Strategies for Enhancing the Breadth of T Cell Responses and Targeting Protective Epitopes during HIV Vaccination, Collaboration for AIDS Vaccine Discovery Annual Meeting, Seattle, WA, 2 Dec 2010.
16. Immunologic Memory: Balancing Vaccine-Induced Protection vs. Pathology, RAPIDD Workshop on Generation and Maintenance of Immune Memory: Immunologic Models and Epidemiological Consequences, Fred Hutchinson Cancer Research Center, Seattle, WA, 7-8 March 2011.
17. Ignorance, Exhaustion, and Death: Understanding the Balance Between Protective and Pathologic T Cell Immunity, Arizona State University, Tempe, AZ, 31 March 2011.
18. Ignorance, Exhaustion, and Death: Understanding the Balance Between Protective and Pathologic T Cell Immunity, Oregon State University, Corvalis, OR, 16 May 2011.
19. Vaccine Adjuvant Strategies to Promote Mucosal Immunity, OCTAVE Capacity Building Workshop on Innate Immunity and Adjuvant Design, New York, NY, July 2011.
20. All-Trans Retinoic Acid Promotes Increased Effector T Cells at Mucosal Sites and Increased Central Memory Systemic T Cells During Vaccination. Novel Vaccines: Adjuvants & Delivery Systems / ImVacS–the Immunotherapeutics & Vaccine Summit, Cambridge, MA, August 17-18, 2011.

21. Ignorance, Exhaustion, and Death: Understanding the Balance Between Protective and Pathologic T Cell Immunity, Emory University, Atlanta, GA, 25 August 2011.
22. Vaccination Against Infection and Disease: Testing Predictions from Mathematical Models of Infection and Immunity, Systems Approaches in Immunology: Advances and Challenges in Multi-Scale Modeling, Santa Fe, NM January 6-7, 2012.

Research Support

Active:

IDS FHCRC / Virology Division UW 7/1/2011-12/31/2011
(PI: J. Blattman)
"**Proof-of-Concept" Study to Link Immununologic and Epidemiologic Measures of HSV-2 Vaccine Efficacy**
Phase III clinical trials of HSV-2 vaccines have not had a clearly defined endpoint vaccine efficacy. Epidemiological outcomes including protection from infection (as measured by seroconversion) can result in less transmission in populations, while reduction of virus load or suppression of virus reactivation can improve clinical disease symptoms. This proof-of-concept study will explicitly link the immunologic responses induced by vaccination against HSV-2 with epidemiologic parameters (VEs:susceptibility, VEp:pathology/disease, and VEi:transmission/infectivity) of vaccine efficacy in mice challenged with HSV-2.

Arizona State University 8/15/2011-6/30/2014
(PI: J. Blattman)
Start-up funding
Funds to be used in ways that appropriately support laboratory research efforts, including purchasing office and lab equipment, hiring personnel, travel, summer salary, and associated ERE.

Pending:

Burroughs Wellcome Trust 7/1/2012-6/30/2017 (*pending review*)
(PI: J. Blattman)
Understanding Vaccine-Induced T Cell Mediated Immunopathology During Infection.
Although Vaccination is generally thought of as either protective or non-protective, T cell based vaccines for persistent viral infections can sometimes result in adverse outcomes such as an increased risk of infection following exposure or increased pathology during subsequent infection. In this project we will make use of mathematical models closely linked with experimental studies to elucidate the circumstances under which vaccination provides protection and when it increases pathology following subsequent infection. In doing so, these studies will help provide a basis for a quantitative framework for the design of T cell vaccines to chronic infections that optimize protective mechanisms while minimizing pathology.

NIH/NIAID R01 7/1/2012-6/30/2017 (*pending review*)
(PI: R. Strong)
Development of 4E10 Epitope-Scaffolds into Efficient HIV Vaccine Immunogens.
Epitope-scaffold strategies to date have failed to induce broadly neutralizing antibodies against HIV in animal models. One potential reason for this is the inability of such vaccines to engage germline precursor BCR on B cells, and to induce somatic hypermutation and affinity maturation of responses that are required to generate bnAbs. We will develop mice expressing either mature or predicted germline versions of the 4E10 bnAb BCR and test the ability of a panel of developed epitope-scaffold immunogens to engage these cells. Moreover, we will couple this

with extensive biochemical and structural analysis of the BCR/immunogen interaction as the first large scale study relating these properties to in vivo immunogenicity

NIH/NIAID R01 7/1/2012-6/30/2017 (*pending review*)
(PI: J. Blattman)
A Direct Measurement of TCR$\alpha\beta$ Combinatorial Diversity.
Despite the direct estimation of the diversity of TCR a and b chains in the naïve repertoire in man and mice, a direct estimation of TCR combinatorial diversity, due to pairing of different TCR α and β chains, has not been done. We will use deep sequencing technology, which we have helped develop, for TCR CDR3 to analyze the total number of endogenous TCR chains that can pair with a fixed TCR in transgenic mice that express a single TCRα or TCRβ chain. Furthermore, we will use an advanced statistical framework to analyze the TCR distributions obtained in order to provide a comprehensive estimate of total TCR diversity in the naïve T cell repertoire.

Completed:
Cancer Research Institute 7/1/2002-6/30/2005
James E. Siegel Perpetual Fellowship Award
(PI: J. Blattman)
Enhancing the Survival and Efficacy of Adoptively Transferred CD8 T Cells during Immunotherapy of Viral Infection and Tumors.
Evaluate strategies to abrogate Cbl-b in CD8 T cells as a means to increase autocrine IL-2 production and enhance efficacy of adoptive immunotherapy of tumors and viral infection.

NIH K01 CA117985-01 7/01/2006-6/30/2011 75%
(PI: J. Blattman)
Enhancing CD8 T Cell Function by Abrogating Inhibition by Regulatory Proteins.
Evaluate strategies to abrogate inhibition of IL-2 production and/or utilization by negative regulatory proteins (Cbl-b, SHP-1, SOCS-1, PD-1) in CD8 T cells to enhance survival, proliferation, and function during adoptive immunotherapy of tumors and viral infection.

Bill and Melinda Gates Foundation 6/1/2006 – 5/31/2011 95%
(PI: P. Greenberg, Co-PI: J. Blattman)
Defining and Comparing Immunogenicity and Improving Activity of Vaccines by Developing and Employing Novel Mouse Models.
Develop and utilize a mouse model system using genetically modified mice to evaluate the immunogenicity of vaccines, determine the immunologic mechanisms engaged during generation and maintenance of robust systemic and mucosal T cell responses and how these mechanisms can be harnessed to enhance T cell responses.

NIH/NIAID P01 AI27757-17 7/1/2009-6/30/2011
(PI: K. Holmes)
Center for AIDS Research (CFAR)
This Center funds a Developmental Core to fund New Investigators, an Administrative Core, and eight research cores which include Clinical Research, Clinical Retrovirology, Genomics, Molecular Immunology, Biostatistics, Socio-Behavioral Research, and Health Services.
Sub-Project: Supplementary Project I 6/1/2008-5/31/2011 5%
(PI: J. Blattman)
Broadening T Cell Responses During HIV Vaccination.
The purpose of this CFAR supplemental grant is to evaluate strategies to increase the breadth of the T cell response elicited by HIV vaccination, by inclusion of immunogens

derived from conserved regions of the gag protein (or deletion of predicted epitopes from variable regions) in order to facilitate recognition of diverse viral strains as well as to prevent viral escape during infection. Additionally, immunogens are design to give preferential processing to conserved regions of gag to increase immunogenicity.