BIOGRAPHICAL SKETCH

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NAME: Arlene H. Sharpe

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POSITION TITLE: George Fabyan Professor of Comparative Pathology

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Radcliffe College, Cambridge, MA	AB	05/1975	Biochemistry
Harvard University, Cambridge, MA	PhD	05/1981	Microbiology
Harvard Medical School, Boston, MA	MD	05/1982	Medicine

A. Personal Statement

My laboratory investigates T cell costimulation and its immunoregulatory functions. My laboratory focuses on the roles of T cell costimulatory and coinhibitory pathways in regulating immune responses needed for the induction and maintenance of T cell tolerance and effective antimicrobial and antitumor immunity. My laboratory has been at the forefront of this field for two decades. We have discovered T cell costimulatory pathways, and elucidated their functions, including the functions of B7-1 and B7-2, CTLA-4, ICOS, PD-1 and PD-1 ligands. We are also involved in studies aimed at translating fundamental understanding of T cell costimulation into new therapies for autoimmune diseases, viral infections, and cancer. Understanding how costimulatory pathways regulate tissue inflammation, tolerance and anti-tumor immunity is an important aspect of my current research. My laboratory uses genetic approaches to determine the obligatory functions of T cell costimulatory pathways through the generation and analyses of transgenic and knockout mice, and in vivo gene perturbation approaches (using RNAi/CRISPR) in mouse models of autoimmunity, infection and cancer. In addition, we study functions of immunoregulatory pathways in human tissues using histologic, transcriptomic and proteomic approaches. I am board-certified in Anatomic Pathology, and use immunohistologic approaches to study human and mouse tissues.

In addition, I am very dedicated to the teaching and training of the next generation of scientists, as demonstrated by my institutional leadership in teaching in the MD and PhD programs at Harvard Medical School as well as my training/mentoring of MD, MD/PhD, and PhD scientists in the laboratory setting.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2019-Present Member, Broad Institute
2019-Present Academic Editor, Journal of Experimental Medicine
2018-Present Chair, Department of Immunology, HMS
2018 Co-Chair, Department of Microbiology and Immunobiology, HMS
2016-2018 Interim Co-Chair, Department of Microbiology and Immunobiology, HMS
2014-2017 NIAID Council, NIH
2013-Present Reviewer, Stand Up to Cancer
2013-Present Co-Director, Evergrande Center for Immunologic Diseases, HMS and BWH
2013-2019 Associate Member, Broad Institute
2013-2018 Head, Immunology Division, Department of Microbiology and Immunobiology, HMS
2012-2018 Professor of Microbiology and Immunobiology, HMS

2011-2018	Councilor, The American Association of Immunologists
2010-2016	Co-Director, Harvard Institute of Translational Immunology, HMS
2010-2014	Editorial Board Member, Annual Review of Immunology
2010-2012	Member, College of Center for Scientific Review (CSR) Reviewers, NIH
2008-2012	Vice Chair for Education, Faculty Development & Diversity, Department of Pathology, HMS
2008-2011	Member at Large, AAAS Section N (Medical Sciences)
2006-2008	Vice Chair for Education, Department of Pathology, HMS
2004-Present	George Fabyan Professor of Comparative Pathology, HMS
2004-2005	Member and Chair, Hypersensitivity, Allergy and Autoimmunity Study Section, NIH
2003-Present	Professor of Pathology, BWH
2000-2004	Member, Immunological Sciences Study Section, NIH
1999-2003	Acting Director, Immunology Research Division, BWH
1997-Present	Ad hoc reviewer for Nature, Science, Immunity, Journal of Experimental Medicine, Journal of Immunology, Nature Immunology
1995-2003	Associate Professor of Pathology, HMS and BWH
1991-1995	Assistant Professor of Pathology, HMS
1988-1991	Research Associate in Pathology, BWH
1985-1991	Postdoctoral Fellow, The Whitehead Institute, MIT
1983-1985	Resident in Pathology, BWH

Honors (selected)

2020	Fellow, National Academy of Inventors
2020	Richard V. Smalley Memorial Award and Lectureship, Society for Immunotherapy of Cancer
2019	Fellow, American Association for Cancer Research
2018	Member, National Academy of Science
2018	Member, National Academy of Medicine
2017	Recipient, Warren Alpert Foundation Prize
2017-2020	Highly Cited Researcher (top 1%), Thomson Reuters
2016	Citation Laureate, Thomson Reuters
2014-2015	Highly Cited Researcher (top 1%), Thomson Reuters
2014	William B. Coley Award, Cancer Research Institute
2007	Fellow, American Association for Advancement of Science
2006-2016	NIAID MERIT Award, NIH
2006	Distinguished Lecturer, The American Association of Immunologists
1993	Beckman Young Investigator, Beckman Foundation
1986-1994	Lucille P. Markey Scholar in Biomedical Science, Lucille P. Markey Charitable Trust
1975	Member, Phi Beta Kappa
1975	Magna cum laude, Radcliffe College

C. Contributions to Science

1. Defining the functions of the B7-1 and B7-2 pathway in T cell activation and tolerance. Our studies of B7-1 deficient mice provided the first *in vivo* evidence for the existence of alternative CTLA4 counter-receptors. As a result, a second CTLA4 counter-receptor, B7-2, was cloned. Our studies revealed that B7-2 is the major early activating costimulator for initiating immune responses. The discovery of B7-2 led us to compare B7-1 and B7-2 functions. We found that B7-1 and B7-2 have critical, overlapping roles in germinal center formation and Ig class switching *in vivo*, and both contribute to T helper cell differentiation. In the mouse model of Multiple Sclerosis, experimental autoimmune encephalomyelitis (EAE), we found that B7-1 and B7-2 have critical overlapping roles not only in the initial activation and expansion of self-reactive T cells, but also in the effector phase of encephalitogenic T cell activation within the central nervous system. The role for B7-1/B7-2 costimulation during the effector phase of autoimmune disease had not been appreciated previously. These findings inspired development of pathway antagonists to block pathogenic T cell responses.

a. Freeman GJ, Borriello F, Hodes RJ, Reiser H, Hathcock KS, Laszlo G, McKnight AJ, Kim J, Du L, Lombard DB, Gray GS, Nadler LM, Sharpe AH. Uncovering of functional alternative CTLA-4 counter-receptor in B7-deficient mice. *Science.* 1993, 262**,** 907-9.
b. Freeman GJ, Borriello F, Hodes RJ, Reiser H, Gribben JG, Ng JW, Kim J, Goldberg JM, Hathcock K, Laszlo G., Lombard LA, Wang S, Gray GS, Nadler LM, Sharpe AH. Murine B7-2, an alternative CTLA4 counter-receptor that costimulates T cell proliferation and interleukin 2 production. *J Exp Med.* 1993, 178**,** 2185-92.

c. Borriello F, Sethna MP, Boyd SD, Schweitzer AN, Tivol EA, Jacoby D, Strom TB, Simpson EM, Freeman GJ & Sharpe AH. B7-1 and B7-2 have overlapping, critical roles in immunoglobulin class switching and germinal center formation. *Immunity.* 1997, 6**,** 303-13.
d. Chang TT, Jabs C, Sobel RA, Kuchroo VK & Sharpe AH. Studies in B7-deficient mice reveal a critical role for B7 costimulation in both induction and effector phases of experimental autoimmune encephalomyelitis. *J Exp Med.* 1999, 190**,** 733-40.

2. Defining the critical inhibitory functions of CTLA-4 in vivo. Our studies with CTLA-4 deficient mice revealed the critical function inhibitory function for CTLA-4, and a previously unsuspected means by which costimulation can regulate responses, showing that costimulation can have both positive and negative regulatory roles. The phenotype of the CTLA-4 deficient mouse strain suggested a critical role for CTLA-4 in regulating T cell tolerance, and prompted studies investigating this issue. We demonstrated an essential role for CTLA-4 in regulating the induction of anergy *in vivo.* More recently, we generated CTLA-4 conditionally deficient mice and used them to dissect CTLA-4 function CD4+ FoxP3- T cells and regulatory cells (Tfr).

a. Tivol EA, Borriello F, Schweitzer AN, Lynch WP, Bluestone JA & Sharpe AH. Loss of CTLA-4 leads to massive lymphoproliferation and fatal multiorgan tissue destruction, revealing a critical negative regulatory role of CTLA-4. *Immunity.* 1995, 3, 541-7.
b. Greenwald RJ, Boussiotis VA, Lorsbach RB, Abbas AK & Sharpe AH. CTLA-4 regulates induction of anergy in vivo. *Immunity.* 2001, 14, 145-55.
c. Cooper ZA, Juneja VR, Sage PT, Frederick DT, Piris A, Mitra D, Lo JA, Hodi S, Freeman GJ, Bosenberg MW, McMahon M, Flaherty KT, Fisher DE, Sharpe AH*, Wargo JA* (*co –senior authors). Response to BRAF inhibition in melanoma is enhanced when combined with immune checkpoint blockade. Cancer Immunology Research. 2014; 2: 643-54. PMC4097121
d. Paterson AM, Lovitch SB, Sage PT, Juneja VR, Lee Y, Trombley JD, Arancibia-Cárcamo CV, Sobel RA, Rudensky AY, Kuchroo VK, Freeman GJ, Sharpe AH. Deletion of CTLA-4 on regulatory T cells during adulthood leads to resistance to autoimmunity. J Exp Med. 2015 Sep 21;212(10):1603-21. PMC4577848

3. Defining the role of PD-1 and its ligands in regulating T cell activation, tolerance and exhaustion. Our studies first demonstrated that PD-L1 and PD-L2 can inhibit T cell proliferation and cytokine production *in vitro*. We determined that the PD-1:PD-L pathway exerts critical inhibitory functions in T cell activation, tolerance, chronic viral infections and tumors. We also showed that PD-L1 is expressed on tumors. We demonstrated that this pathway controls multiple tolerance checkpoints that prevent autoimmunity: restraining initial activation of self-reactive T cells, limiting pathogenic effector cells, and promoting and sustaining regulatory T cells. We also identified a novel role for PD-L1 on non-hematopoietic cells in regulating self-reactive T cells. In collaboration with the laboratories of Drs. Rafi Ahmed and Gordon Freeman, we discovered that the PD-1:PD-L1 pathway contributes directly to T cell exhaustion and lack of viral control during chronic LCMV infection. These studies revealed the therapeutic potential for this pathway for treating T cell exhaustion and have translated into clinical trials and cancer immunotherapy. We are currently investigating other coinhibitory pathways and their interplay with the PD-1 pathway in tolerance, infection and cancer.

a. Latchman Y, Wood CR, Chernova T, Chaudhary D, Borde M, Chernova I, Iwai Y, Long AJ, Brown JA, Nunes R, Greenfield EA, Bourque K, Boussiotis VA, Carter LL, Carreno BM, Malenkovich N, Nishimura H, Okazaki T, Honjo T, *Sharpe AH, *Freeman GJ & *Co-Senior Authors. PD-L2 is a second ligand for PD-1 and inhibits T cell activation. *Nat Immunol.* 2001, 2**,** 261-8.
b. Keir ME, Liang SC, Guleria I, Latchman YE, Qipo A, Albacker LA, Koulmanda M, Freeman GJ, Sayegh MH & Sharpe AH. Tissue expression of PD-L1 mediates peripheral T cell tolerance. *J Exp Med.* 2006, 203**,** 883-95. PMC2118286
c. Barber DL, Wherry EJ, Masopust D, Zhu B, Allison JP, Sharpe AH, Freeman GJ & Ahmed R. Restoring function in exhausted CD8 T cells during chronic viral infection. *Nature.* 2006, 439**,** 682-7.
d. Juneja VR, McGuire KA, Manguso RT, LaFleur MW, Collins N, Haining WN, Freeman GJ, Sharpe AH. PD-L1 on tumor cells is sufficient for immune evasion in immunogenic tumors and inhibits CD8 T cell cytotoxicity. J Exp Med. 2017 Apr 3;214(4):895-904. PMC5379970

4. Defining the functions of T follicular regulatory cells (Tfr). Tfr cells are a newly discovered Treg subset that inhibits humoral immunity. We have developed methods to determine mechanisms of Tfr cell suppression, and found that Tfr cells can prevent activation of both Tfh and B cells. By separating analyzing Tfh and Tfr cells, we determined that Tfr cell differentiation is restrained by PD-1 and CTLA-4. We also found that PD-1 inhibits Tfr suppressive function, while CTLA-4 is a mediator of Tfr suppressive capacity.

a. Sage PT, Francisco LM, Carman CV, Sharpe AH. The receptor PD-1 controls follicular regulatory T cells in the lymph nodes and blood. Nat Immunol. 2013 Feb; 14(2):152-61. PMC3788614

b. Sage PT, Paterson AM, Lovitch SB, Sharpe AH. The Coinhibitory Receptor CTLA-4 Controls B Cell Responses by Modulating T Follicular Helper, T Follicular Regulatory, and T Regulatory Cells. Immunity. 2014; 41(6):1026-1039. PMC4309019
c. Sage PT, Ron-Harel N, Juneja VR, Sen D, Maleri S, Sungnak W, Kuchroo VK. Haining WN, Chevrier N, Haigis MC, Sharpe AH TFR Cell Suppression Leads to Durable and Selective Inhibition of B Cell Effector Functions. 2016. *Nature Immunology*, 17: 1436-46. PMC5502675.
d. Sage PT, Tan CL, Freeman GJ, Haigis M, Sharpe AH. Defective TFH Cell Function and Increased TFR Cells Contribute to Defective Antibody Production in Aging. Cell Rep. 2015 Jul 14;12(2):163-71. PMID: 26146074

5. Defining regulators of immunity using in vivo CRISPR screens. We have developed a system for perturbation of genes in immune cells *in vivo* using CRISPR-Cas9. This system expands the breadth of immune lineages that can be edited including naïve T and B cells, macrophages and dendritic cells, and enables in vivo pooled screens to discover immunoregulatory genes and knockout individual genes to characterize their function.

a. LaFleur MW, Nguyen TH, Coxe MA, Yates KB, Trombley JD, Weiss SA, Brown FD, Gillis JE, Coxe DJ, Doench JG, Haining WN, Sharpe AH. A CRISPR-Cas9 delivery system for in vivo screening of genes in the immune system. Nat Commun. 2019 Apr 10;10(1): PMC6458184
b. LaFleur MW, Nguyen TH, Coxe MA, Miller BC, Yate KB, Gillis JE, Sen DR, Gaudiano EF, Al Abosy R, Freeman GJ, Haining WN, Sharpe AH. PTPN2 regulates the generation of exhausted CD8+ T cell subpopulations and restrains tumor immunity. Nature Immunology 2019 Oct; 20: 1360-1371.

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/arlene.sharpe.1/bibliography/public/