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Jonathan S. Bromberg, MD, PhD

Academic Title:

Professor

Primary Appointment:

Surgery

Secondary Appointment(s):

Microbiology and Immunology

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Education and Training

EDUCATION

1970-1973	Wyoming High School, Wyoming, OH
1973-1974	Gresham's School, Holt, Norfolk, England
1974-1977	Harvard College, Cambridge, MA; A.B. (summa cum laude, phi beta kappa, Biology)

1978-1983 Harvard Medical School, Boston, MA; M.D.

1979-1983 Harvard Graduate School of Arts and Sciences, Boston, MA; Ph.D.

(Immunology, Drs. Baruj Benacerraf and Mark Greene)

POSTGRADUATE AND POSTDOCTORAL TRAINING

1977-1978 Postgraduate researcher, ICRF Tumor Immunology Unit, University College, London (Drs. N. Avrion Mitchison and P. Lake)

1983-1988 Intern, resident, chief resident, Department of General Surgery,

University of Washington Affiliated Hospitals, Seattle, WA

1986-1988 Coinvestigator, Human Antigen-Specific T Suppressor Cell Genetic

Markers, University of Washington and Virginia Mason Research

Center, Seattle, WA (Dr. Jerry Nepom)

1988-1990 Fellow, Division of Transplantation, Department of Surgery,

Hospital of the University of Pennsylvania, Philadelphia, PA

Biosketch

A. Personal Statement

I have been involved continuously in basic cellular and molecular transplant immunology for over 25 years and have been continuously funded for the entire time. My basic research has always focused on T cell immunobiology, and for more than 15 years has also focused on issues of migration, trafficking, secondary lymphoid organ structure and function, and lymphatic structure and function, and how these processes and structures influence T cell immunity and T cell tolerance in models of cardiac transplantation and pancreatic islet transplantation. I have also maintained an active clinical practice in solid organ transplantation and am thus constantly exposed to the problems of patients and their immune systems, including cellular and humoral rejection, opportunistic infections, chronic viral disease, autoimmune organ failure, and immunosuppression medication side effects. My basic research and clinical interests are especially well suited to complement and inform each other, and to keep each aspect of my professional life current and relevant.

B. Positions and Honors

Academic Appointments

1988-1990 Clinical Instructor, Hospital of the University of Pennsylvania

1990-1994 Assistant and Associate (1992) Professor of Surgery and Microbiology and Immunology, MUSC

1. Associate Professor and Full Professor (1998) of Surgery and Microbiology and Immunology, University of Michigan

   1999-2010 Professor of Surgery and Gene and Cell Medicine, Chief Kidney/Pancreas Transplantation, Transplant Research, Transplantation Institute, Mount Sinai School of Medicine

   2010-present Professor of Surgery and Microbiology and Immunology, Chief and Director of Research, Division of Transplantation, Director of Strategic Planning for Transplantation Services, University of Maryland School of Medicine

   C. Contributions to Science

   1. Major questions in organ transplant are where does tolerance take place and what processes determine the choice between tolerance and immunity. Using a variety of pharmacologic and genetic approaches in cardiac and islet transplant models, my lab demonstrated that normal lymph node functions and structures are required for tolerance induction and maintenance. We demonstrated the requirement for CD4+ T cell migration from

blood into lymph nodes, regulated by a variety of selectins, integrins, and chemokines, that determine T cell anergy, apoptosis, and regulatory T cell induction and suppression. In addition, plasmacytoid dendritic cells (pDC) are also required to migrate into lymph nodes and present alloantigen to T cells. These studies provided novel evidence for active roles of the lymph node in determining the fate of T cells and the immune response.

a. Bai, Y, Liu, J, Wang, Y, Honig, S, Qin, L, Boros, P, Bromberg, JS. L-selectin dependent lymphoid occupancy is required to induce alloantigen specific tolerance. J. Immunol., 2002, 168:1579-1589.

b. Ochando, JC, Yopp, AC, Yang, Y, Li, Y, Boros P, Llodra, J, Ding, Y, Krieger, N, Bromberg, JS. Lymph node occupancy is required for the peripheral development of alloantigen-specific Foxp3+ regulatory T cells. J. Immunol., 2005, 174:6993-7005. PMID: 15905542

c. Ochando JC, Homma C, Yang Y, Hidalgo A, Garin A, Tacke F, Angeli V, Li Y, Boros P, Ding Y, Jessberger R, Lira SA, Randolph GJ, and Bromberg JS, Alloantigen-presenting plasmacytoid dendritic cells mediate tolerance to vascularized grafts. Nature Immunol., 2006, 7:652-662. PMID: 16633346

d. Burrell, BE, Bromberg, JS. Fates of CD4+ T cells in a tolerant environment depend on timing and place of antigen exposure. Am. J. Transplant., 2012, 12:576-589. PMID: 22176785

2. The understanding of induction, stimulation, maintenance, and activity of FoxP3+ CD4+ suppressive regulatory T cells (Treg) is critical to manipulating immunity. We were one of the first to demonstrate that TGFb is required for Treg induction, and that inflammatory stimuli and cytokines can inhibit Foxp3 induction or stability. Epigenetic regulation of the Foxp3 gene is critical for Treg activity, and Foxp3 gene expression and structure can be manipulated with T cell receptor and costimulatory signals, cytokine and TLR signals, and methyltransferase inhibitors. These results were extended to the generation of human Tregs in vitro for therapeutic use. We also demonstrated critical roles for IL10, TGFb, and the induction of myeloid derived suppressor cells in the mechanisms of Treg suppression and tolerance. These studies defined important pharmacologic modulators of Treg that can be translated into clinically relevant approaches for therapy.

a. Fu S, Yopp AC, Mao M, Chen D, Zhang H, Chen D, Bromberg JS. TGF-b induces Foxp3+ T regulatory cells from CD4+CD25- precursors. Am.J.Transplant., 2004, 4:1614-1627. PMID: 15367216

b. Lal G, Zhang N, van der Touw W, Ding Y, Ju W, Bottinger E, Reid SP, Levy DE, Bromberg JS. Epigenetic regulation of Foxp3 expression in regulatory T cells by DNA methylation. J. Immunol., 2009, 182:259-273. PMID: 19109157

c. Rodriguez Garcia M, Ledgerwood L, Yang Y, Xu J, Lal G, Burrell B, Ma G, Grisotto M, Hashimoto D, Li Y, Boros P, van Rooijen N, Matesanz R, Tacke R, Ginhoux F, Ding Y, Chen S-H, Randolph G, Merad M, Bromberg JS, Ochando J. Monocytic suppressive cells mediate transplantation tolerance in mice. J. Clin. Invest., 2010, 120:2486-2496. PMID: 20551515

d. Hippen, KL, Merkel, SC, Schirm, DK, Sieben, CM, Sumstad, D, Kadidlo, DM, McKenna, DH, Bromberg, JS, Levine, BL, Riley, JL, June, CH, Miller, JS, Wagner, JE, Blazar, BR. Massive ex vivo expansion of human natural regulatory T cells (Tregs) with minimal loss of in vivo functional activity. Sci. Transl. Med., 2011, 3:83ra41. PMID: 21593401

3. A major issue concerning Treg suppressive and tolerogenic competence is to discover how to deliver these cells to the right place at the right time. My lab was the first to demonstrate that Treg not only must be induced in lymph nodes, but also must migration from tissues through afferent lymphatics into lymph nodes in order to fully suppress inflammation and immunity and prolong islet allograft survival. Lymphatic migration is regulated by a number of integrins, selectins, chemokines, and sphingosine 1-phospate receptors (S1PR) on the T cell. Treg interact with endothelial cells, parenchymal cells, and antigen presenting cells during their migration, effecting distinct suppressive activities required for graft survival and required for the induction and maintenance of Treg activation and suppressive function. These studies defined novel aspects of Treg

function that point toward therapeutically important implications for manipulating immunity and suppression.

The structure and function of lymphatic vessels are poorly understood, in large part due to the difficulty of isolating these cells for in vitro work and manipulating and imaging these structures in vivo. Our studies on Treg migration led to more general studies of lymphatic function. We defined a stable lymphatic endothelial cell (LEC) line that recapitulates LEC function in vitro, allowing ablumenal-to-lumenal migration to a chemokine gradient, but not the reverse migration. In contrast, blood endothelial cells permit migration in both directions. A sphingosine 1-phosphate (S1P) gradient promotes transendothelial migration across LEC, while a high concentration of S1P, such as occurs in acute inflammation, inhibits afferent lymphatic migration, retaining immune cells in tissues. Lymphangiogenesis not only occurs in the presence of inflammation, but also promotes inflammation and can be targeted to prevent allograft rejection. These studies defined new tools for lymphatic research and defined potential novel therapeutic approaches to modulating inflammation.

a. Zhang N, Schroppel B, Lal G, Jakubzick C, Mao X, Chen D, Jessberger R, Ochando JC, Bromberg JS. Regulatory T cells sequentially migrate from the site of tissue inflammation to the draining LN to suppress allograft rejection. Immunity, 2009, 30:458-469. PMID: 19303390

b. Lal, G, Yin, N, Xu, J, Lin, M, Schroppel, B, Ding, Y, Marie, I, Levy, DE, Bromberg, JS. Distinct inflammatory signals have physiologically divergent effects on epigenetic regulation of Foxp3 expression and Treg function. Am. J. Transplant., 2011, 11:203-214. PMID: 21219575

c. Ledgerwood, LG, Lal, G, Zhang, N, Garin, A, Esses, SJ, Ginhoux, F, Peche, H, Lira, SA, Ding, Y, Yang, Y, He, X, Schuchman, EH, Allende, ML, Ochando, JC, Bromberg, JS. Sphingosine 1-phosphate receptor S1P1 causes tissue retention by inhibiting peripheral tissue T lymphocyte entry into afferent lymphatics. Nature Immunol., 2008, 9:42-53. PMID: 18037890

d. Brinkman CC, Iwami D, Hritzko MK, Xiong, Y Ahmad, Bromberg JS. Treg engage lymphotoxin beta receptor for afferent lymphatic transendothelial migration. Nature Communications 2106; 7:12021. PMID: 27323847

4. The recognition that lymph nodes are required for tolerance and that there are distinct domains within the lymph node committed to different aspects of immunity, led to investigations of other discrete cells and structures, their regulation, and their roles in immunity and tolerance. During tolerization we showed that alloantigen specific Treg and pDC presenting specific alloantigen were concentration around the cortical ridge, an area that encompasses the high endothelial venules and is a site for trafficking into the lymph node between the cortex and medulla. During tolerance there is increased laminin a4 and decreased laminin a5 in the cortical ridge, while during immunity the ratios are reversed. There is a role for fibroblastic reticular cells in regulating lymph node structure and cytokines, antigen presentation, and tolerance. Other stromal fibers, such as ERTR-7, also dictate CD4+ T cell, Treg, and pDC movements and the choice between tolerance and immunity. These studies defined novel roles for stromal fibers, stromal cells, and the cortical ridge in tolerance.

a. Warren, KJ, Iwami, D, Harris, DG, Bromberg, JS, Burrell, BE. Vascular basement membrane proteins laminin alpha 4 and laminin alpha 5 differentially influence CD4+ T cell lymph node trafficking and allograft fate. J. Clin. Invest., 2014, 124:2204-2218. PMID: 24691446

b. Nakayama, Y, Bromberg, JS. Murine lymphotoxin-beta receptor signaling regulates stromal cell chemokine expression and neutrophil trafficking required for tolerance. Am. J. Transplant., 2012, 12: 2322 – 2334. PMID: 22594431

c. Burrell BE, Warren KJ, Nakayama Y, Iwami, D, Brinkman, CC, Bromberg JS. The lymph node stromal fiber (ER-TR7) functions to modulate CD4+ T cell lymph node trafficking and transplant tolerance. Transplantation, 2015, 99:1119-1125. PMID: 25769074

d. Tostanoski LH, Chui Y-C, Gammon JM, Simon T, Andorko J, Bromberg JS, Jewell CM. Reprogramming the local lymph node microenvironment during autoimmunity promotes systemic, yet antigen-specific tolerance. Cell Reports 2016, 16:2940 – 2952. PMID: 27626664

5. The discovery of the role of S1PR in leukocyte-transendothelial migration has recently opened up new areas of investigation to uncover the role of S1P and S1PR in diverse aspects of immunity and inflammation. We assessed the role of the major T cell S1PR1 receptor in migration, immunity, and tolerance. We uncovered novel activities for the S1PR agonist/antagonist FTY20 in modulating lymph node versus splenic migration, and immunity versus tolerance. My lab discovered that S1PR signaling involves a complex cascade, engaging multidrug transporters and cysteinyl leukotriene synthesis and transport to fully effect changes in lymphocyte migration. S1P acts as both a chemotactic cytokine and as an inhibitor of migration, depending on concentration and gradients. Targeting S1PR promotes graft survival and tolerance. These studies defined novel aspects of S1P and S1PR metabolism and function and shed new light on how activators and inhibitors may have highly complex effects in vivo.

a. Bai, Y, Liu, J, Wang, Y, Honig, S, Qin, L, Boros, P, Bromberg, JS. L-selectin dependent lymphoid occupancy is required to induce alloantigen specific tolerance. J. Immunol., 2002, 168:1579-1589. PMID: 11823485

b. Honig SM, Fu S, Mao X, Yopp A, Gunn MD, Randolph GJ, Bromberg JS. FTY720 stimulates multidrug transporter and cysteinyl leukotriene dependent T cell chemotaxis to lymph nodes. J. Clin. Invest., 2003, 11:627-637. PMID: 12618517

c. Yopp AC, Ochando JC, Mao M, Ledgerwood L, Ding Y, Bromberg JS. Sphingosine 1-phosphate receptors regulate chemokine driven transendothelial migration of lymph node but not splenic T cells. J. Immunol., 2005, 175:2913-2924. PMID: 16116177

d. Ledgerwood, LG, Lal, G, Zhang, N, Garin, A, Esses, SJ, Ginhoux, F, Peche, H, Lira, SA, Ding, Y, Yang, Y, He, X, Schuchman, EH, Allende, ML, Ochando, JC, Bromberg, JS. Sphingosine 1-phosphate receptor S1P1 causes tissue retention by inhibiting peripheral tissue T lymphocyte entry into afferent lymphatics. Nature Immunol., 2008, 9:42-53. PMID: 18037890

Link to my full CV:

http://www.ncbi.nlm.nih.gov/sites/myncbi/jonathan.bromberg.1/bibliography/41147754/public/?sort=date&direction=ascending

Research/Clinical Keywords

Transplantation, Immunology, Tolerance, Migration, Microbiota

Highlighted Publications

Tostanoski LH, Chui Y-C, Gammon JM, Simon T, Andorko J, **Bromberg JS**, Jewell CM. Reprogramming the local lymph node microenvironment during autoimmunity promotes systemic, yet antigen-specific tolerance. Cell Reports 2016, 16:2940–2952. PMID: 27626664

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Yin, N, Zhang, N, Lal, G, Xu, J, Yan, M, Ding, Y, Bromberg, JS. Lymphangiogenesis is required for pancreatic islet inflammation and diabetes. PLoS ONE, 2011, 6 (11):e28023. PMID: 22132197 Warren, KJ, Iwami, D, Harris, DG, Bromberg, JS, Burrell, BE. Vascular basement membrane proteins laminin alpha 4 and laminin alpha 5 differentially influence CD4+ T cell lymph node trafficking and allograft fate. J. Clin. Invest., 2014, 124:2204-2218. PMID: 24691446

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Burrell BE, Warren KJ, Nakayama Y, Iwami, D, Brinkman, CC, Bromberg JS. The lymph node stromal fiber (ER-TR7) functions to modulate CD4+ T cell lymph node trafficking and transplant tolerance. Transplantation, 2015, in press. PMID: 25769074

Nakayama Y, Brinkmann, CC, Bromberg JS. Murine fibroblastic reticular cells from lymph node interact with CD4+ T cells through CD40-CD40L. Transplantation, 2015, in press. PMID: 25856408

Bai, Y, Liu, J, Wang, Y, Honig, S, Qin, L, Boros, P, Bromberg, JS. L-selectin dependent lymphoid occupancy is required to induce alloantigen specific tolerance. J. Immunol., 2002, 168:1579-1589. PMID: 11823485

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