OMB No. 0925-0001 and 0925-0002 (Rev. 10/2021 Approved Through 01/31/2026)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.  
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NAME: Jonathan S. Bromberg

eRA COMMONS USER NAME (credential, e.g., agency login): JONBROMBERG

POSITION TITLE: Professor of Surgery and Microbiology and Immunology; Vice Chair for Research

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 |
| --- | --- | --- | --- |
| Harvard College, Cambridge, MA  Harvard Medical School, Boston, MA  Harvard Graduate School of Arts and Sciences | A.B.  M.D.  Ph. D. | 06/1977  06/1983  06/1983 | Biology  Medicine  Immunobiology |

**A. Personal Statement**

I have been involved continuously in basic cellular and molecular transplant immunology for 30 years and have been continuously funded for the entire time. My basic research has always focused on T cell immunobiology, and for more than 20 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 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. I have had over 60 trainees in my lab, am actively involved in teaching and mentoring, and have served on T32 faculty.

**Ongoing and Completed Research Support**

5 U01 DK116095-06 (Bromberg) 07/01/23-05/31/28

**Trans-omics Analysis of African American Deceased Donor Kidneys for Transplant Outcomes**

The goals of the project are: Aim 1. To prospectively collect long-term follow-up data on all APOLLO participants. Aim 2. To provide detailed clinical data and biospecimens on APOLLO participants from our Clinical Center. Aim 3. To facilitate return of APOL1 genotype results.

5 R01 EB0271434 (Jewell) 03/15/2019-11/30/2022 **Programming immune function through modular assembly of polyionic immune signals**

The goal of this project is to use self-assembly of immune signals for programmable activation of defined combinations of stimulatory immune pathways to enhance adjuvant function.

5 R01 AI144667-04 (Jewell) 06/17/2019-05/31/2024 **Improving multiple sclerosis patient quality of life using microneedle patches for delivery of MS drugs** The goal of this project is to build easily-administered patches from existing human multiple sclerosis drugs to enable patients with reduced motor skills to effectively self-administered MS drugs.

5 R01 HL1486724 (Bromberg) 07/15/2019-06/30/2023 **Immunological and functional consequences triggered by the gut microbiota regulate alloimmunity and cardiac transplant outcomes**

This proposal will take advantage of our expertise in microbiota analysis and in molecular and cellular transplant immunology. The definition of pro-inflammatory and anti-inflammatory microbiota and strains may provide a precise platform to define the most important upstream influences that initiate organ inflammation and scarring and could serve as potent diagnostic markers for allograft management.

2 R01 AI114496-06A1 (Bromberg) 04/20/2015-05/31/2025 **Lymph Node Structure and Function in Tolerance: Role of Laminins**

This project will demonstrate that pro-inflammatory LN structures accentuate transplant rejection. We intend to define both the mechanisms of stromal cell responses and specific immunosuppression that results in LN structures that support tolerogenic immune responses.

1 P01AI153003-03 (Abdi) (Project 2 Bromberg) 07/27/2020-06/30/2025 **Lymph nodes at the crossroads of allo immunity and regulation, Project 2: Reshaping lymph node stroma for transplant tolerance**

This proposal establishes a multidisciplinary collaborative team to produce novel mechanistic data, which will provide the basis for highly innovative and selective therapeutic strategies for transplantation. This proposal can make transformative advances in the field of organ transplantation.

7 RO1DK122682-02 (Mas) 07/01/2019-06/30/2024 **Dissecting the role of dynamic epigenome prompting pathways leading to kidney allograft fibrosis**

The proposed studies will provide information about the effect of epigenetic modifications on molecular pathways and upstream regulators leading to CAD. Resulting non-invasive biomarkers will better predict and stratify graft injury and fibrosis progression, potentially improving long-term renal graft outcomes.

R37AI062765-17A1 (Bromberg) 4/2/2020-4/1/2025

**Regulatory T Cells and Lymphatic Endothelial Cells: Regulatory Interactions for Migration and Suppression.**

This proposal will deemonstrate that LT- LTR and PD-1-PD-L1 interactions regulate Treg migration, homeostasis, function, and the interaction with lymphatic endothelium.

I01BX003690-06A1 (Jewell) 07/01/2022-09/30/2026

**Tunable Assembly of Regulatory Immune Signals to Promote Myelin-specific Tolerance**

The proposal will characterize iPEM material properties and screen in primary mouse cells and MS patient samples; assess potency in progressive autoimmune disease (EAE) and test if tolerance is myelin-specific; elucidate the structural and functional changes in LNs, spleen, and the CNS that lead to tolerance; and test if tolerance is generalizable to other self-antigens using relapsing-remitting model (RR-EAE).

1R01AI169686 (Jewell) 02/01/2022-01/31/2027

**Defining the induction and maintenance of myelin-specific tolerance in T cells and B cells using local lymph node depots**

The proposal will: Define the robustness of efficacy and the underpinning therapeutic effects on neuroinflammation; Show the durability of tolerance is antigen-dependent and driven by TREG maintenance & plasticity; and Show i.LN. depots disrupt germinal centers, reduce auto-antibodies, & induce tolerogenic B cells.

U01AI170050 (Bromberg, Co-PI) 05/13/2022-04/30/2027

**Mechanisms of microbiome-driven cardiac allograft outcomes**

The proposal will: Elucidate the molecular mechanisms by which the gut microbiome determines cardiac allograft outcomes; Determine intestinal epithelial cell type-specific responses to pro- or anti-inflammatory bacterial induction; and Define microbiome-driven immune responses and LN structural changes that determine cardiac graft outcomes.

**Citations:**

1. 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.
2. 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. PMCID: PMC4001556.
3. Piao W, Xiong Y, Famulski K, Brinkman CC, Li L, Wagner C, Saxena V, Simon T, Bromberg JS. Regulation of T cell afferent lymphatic migration by targeting LTR-mediated non-classical NFB signaling. Nature Comm. 2018, 9: 3020. doi: 10.1038/s41467-018-05412-0. PMCID: PMC6070541.
4. Xiong Y, Piao W, Brinkman CC, Li L, Kulinski JM, Olivera A, Cartier A, Hla T, Hippen K, Blazar B, Schwab SR, Bromberg JS. CD4 T cell Sphingosine 1-phosphate receptor (S1PR)1 and S1PR4 and endothelial S1PR2 regulate afferent lymphatic migration. Science Immunology 2019, Mar 15;4(33)eeav1263. doi: 10.1126/sciimmunol.aav1263. PMCID: PMC6744614.

**B. Positions, Scientific Appointments, and Honors**

**Positions and Scientific Appointments**

2021–present Adjunct Professor, Department of Bioengineering, University of Maryland, College Park, MD

2010-present Professor of Surgery and Microbiology and Immunology, Chief, Director of Transplant Research, Vice Chair for Research Department of Surgery, University of Maryland

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

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

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

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

**Postgraduate and Postdoctoral Training**

1988-1990 Transplant Fellow, Department of Surgery, University of Pennsylvania, Philadelphia, PA

1983-1988 Resident, Department of General Surgery, University of Washington, Seattle, WA

1977-1978 Postgraduate researcher, ICRF Tumor Immunology Unit, University College, London

**Honors and Awards**

2021-MERIT Award NIAID; 2014-NKF of Maryland, Kidney Champion Award; 2014-present-*Transplantation*, Clinical Sciences Executive Editor; 2013-AST Basic Science Established Investigator Award; 2002–Lazarovits Commemorative Lecture, Canadian Society of Transplantation; 2000-2005-Journal of Immunology, Section Editor; 2000-2014-*American Journal of Transplantation*, Associate Editor, Deputy Editor, Section Editor for Literature Watch; 1992-present: NIAID, NIDCR, SAT, TTT, and SBIR study sections; 2001-Roslyn Commemorative Lecture, Society of University Surgeons; 1997-Excellence in reviewing, Journal of Surgical Research; 1998-ASTS Roche Presidential Travel Award; 1992-Thomas A. and Shirley W. Roe Foundation Award; 1992-94 American Surgical Association Foundation Fellowship Award; 1988-90-Sandoz Award, American Society of Transplant Surgeons; 1983-James Tolbert Shipley Prize; 1979-83-Medical Scientist Training Program Fellowship; 1977-Detur Book Prize; 1977-Summa Cum Laude, Biology; 1976-Phi Beta Kappa; 1975,76,77-John Harvard Award; 1975-Edwards-Whitaker Award

**Recent Grant Review Committees and Boards**

2022-present Peer Reviewed Medical Research Program (PRMRP) for the Department of Defense Congressionally Directed Medical Research Programs (CDMRP), Reconstructive Transplant Research Program, Programmatic Panel Member

2022 SEP ZRG1 IDIB-J (02) M HIVD

2021 SEP SRG 2021/05 TTT

2021 SEP SRG 2021/10 ZAI1 LAR-X (M1) 1, PAR-20-072

2021 ACTS Study Section, 2021/10 ACTS, ZRG1 ACTS-L (07) S

2021 MCBS Study Section, 2022/01 MCBS (JA) 1, NHLBI

2020 Immune Tolerance Network 10 ZAI1 TC-I (S3) R

2020 ZRG1 IMM-C02 M Special Emphasis Panel (SEP), chair

2020 Sir Charles Gairdner and Osborne Park Health Care Group (SCGOPHCG), Charlies Foundation for Research

2020 British Heart Foundation Clinical Study Grant

2020 NIAID Special Emphasis Panel/Scientific Review Group 2020/05 ZAI1 JTS-I (M1) 2

2019 KDIGO Nomenclature Consensus Conference

2018 NIAID Clinical Trial Planning Grants (R34) 201810 ZAI1 TC-I (S1) 1 Review Committee, Chair

2018 CDRMP Reconstructive Transplant Research Program (RTRP) Immune System Regulation (ISR), Chair

**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 pharmacologic and genetic approaches, 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, Bromberg JS. Alloantigen-presenting plasmacytoid dendritic cells mediate tolerance to vascularized grafts. Nature Immunol., 2006, 7:652-662. PMID: 16633346

**d.** Piao W, Li L, Saxena V, Iyyathurai J, Lakhan R, Zhang Y, Tadeval Lape I, Paluskievicz C, Hippen KL, Lee Y, Silverman E, Willsonshirky M, Riella RV, Blazar BR, Bromberg JS. PD-L1 signaling selectively regulates lymphatic transendothelial migration. Nature Communications 2022, 13:2176. PMID: 35449134

**2.** The understanding of **induction, stimulation, maintenance, and activity of FoxP3+ CD4+ suppressive regulatory T cells (Treg)** is critical to manipulating immunity. We were among the first to demonstrate that TGF 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, TGF, 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.** 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. PMCID: 3731994.

**b.** 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. PMCID: PMC2898596.

**c.** 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. PMCID: PMC3551476.

**d.** Saxena V, Piao W, Li L, Paluskievicz C, Xiong Y, Simon T, Lakhan R, Brinkman CC, Walden S, Hippen KL, WillsonShirkey M, Lee YS, Wagner C, Blazar BR, Bromberg JS. Treg tissue stability depends on lymphotoxin beta receptor- and adenosine receptor-driven lymphatic endothelial cell responses. Cell Reports 2022, 39: 110727. PMID: 35443187

**3.** My lab was the first to demonstrate that **Treg not only must be induced in lymph nodes, but also must migrate from tissues through afferent lymphatics into lymph nodes** to fully suppress inflammation and immunity and prolong allograft survival. Lymphatic migration is regulated by several integrins, selectins, chemokines, and sphingosine 1-phospate receptors (S1PR). Treg interact with endothelial cells, parenchymal cells, and antigen presenting cells during their migration, effecting distinct suppressive activities required for graft survival and the induction and maintenance of Treg activation and suppressive function. These studies defined therapeutically important implications for manipulating immunity and suppression.

The structure and function of lymphatic vessels are poorly understood. **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. An 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 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. PMCID: PMC2737741.

**b.** 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.

**c.** Brinkman CC, Iwami D, Hritzko MK, Xiong, Y Ahmad, Bromberg JS.. Treg engage lymphotoxin beta receptor for afferent lymphatic transendothelial migration. Nature Communications 2016; 7:12021. PMCID: PMC4919545.

**d.** Piao W, Xiong Y, Famulski K, Brinkman CC, Li L, Wagner C, Saxena V, Simon T, Bromberg JS. Regulation of T cell afferent lymphatic migration by targeting LTR-mediated non-classical NFB signaling. Nature Comm. 2018, 9: 3020. doi: 10.1038/s41467-018-05412-0. PMCID: PMC6070541.

**4.** Lymph nodes are required for tolerance and there are **distinct domains within the lymph node committed to different aspects of immunity**. During tolerization alloantigen specific Treg and pDC presenting specific alloantigen concentrate 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 4 and decreased laminin 5 in the cortical ridge, while during immunity the ratios are reversed. Fibroblastic reticular cells regulate 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. PMCID: PMC4001556.

**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. PMCID: PMC3424360.

**c.** 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. PMCID: PMC5024722.

**d.** Li L, Willsonshirkey M, Zhang T, Xiong Y, Piao W, Saxena V, Paluskievicz C, Lee Y, Toney N, Cerel BM, Li Q, Simon T, Smith KD, Hippen KL, Blazar BR, Abdi R, Bromberg JS. The lymph node stromal laminin 5 shapes alloimmunity. J Clin Invest 2020, 130:2602-2619. PMID: 32597832

**5.** **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.** 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. PMCID: PMC151892.

**b.** 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.

**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.** Xiong Y, Piao W, Brinkman CC, Li L, Kulinski JM, Olivera A, Cartier A, Hla T, Hippen K, Blazar B, Schwab SR, Bromberg JS. CD4 T cell Sphingosine 1-phosphate receptor (S1PR)1 and S1PR4 and endothelial S1PR2 regulate afferent lymphatic migration. Science Immunology 2019, Mar 15;4(33)eeav1263. doi: 10.1126/sciimmunol.aav1263. PMCID: PMC6744614.

Link to my full CV: <https://www.ncbi.nlm.nih.gov/myncbi/jonathan.bromberg.1/bibliography/public/>