BIOGRAPHICAL SKETCH

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NAME: Todd Victor Brennan

eRA COMMONS USER NAME (agency login): TODDBRENNAN

POSITION TITLE: Associate Professor of Surgery

EDUCATION/TRAINING:

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
University of California, Los Angeles, Los Angeles, CA	BS	06/1994	Biochemistry
University of California, Los Angeles, Los Angeles, CA	MS	06/1994	Biochemistry
Harvard University, Boston, MA	MD	06/1999	Medicine
University of California, San Francisco, San Francisco, CA	Resident	06/2007	General Surgery
University of California, San Francisco, San Francisco, CA	Fellow	06/2009	Abdominal Transplant Surgery

A. Personal Statement

While nearly 30,000 organ transplants are performed in the United States each year, the waitlist for transplant organs currently exceeds 123,000 individuals and is rising. Despite significant advances in our understanding of immune mechanisms and immunosuppression therapy, 25-40% of grafts will be lost within 5 years of transplantation from immune-mediated graft rejection. Given the shortage of available organs, there is a critical need for improved methods for the detection and prevention of graft rejection. As a transplant surgeon and immunologist, I am keenly interested in discovering methods to increase the viability of transplanted organs in order to improve patient outcomes.

I have a scientific background in biochemistry (1), molecular biology and immunology (2), as well clinical expertise in organ transplantation. My current research is focused on endogenous sources of innate immune activation that arise in the setting of tissue injury. I seek to understand how these molecules lead to the activation of the adaptive immune system that leads to organ rejection (3,4). A better understanding of key mediators of the inflammatory response to tissue injury will highlight novel mechanisms that can be targeted therapeutically to improve graft survival by decreasing rates of graft rejection, at the same time serving as specific biomarkers that can be used to detect early graft rejection.

1. Brennan TV, Lin L, Brandstadter JD, Rendell VV, Dredge K, Huang X, Yang Y. Heparan sulfate mimetic PG545-mediated antilymphoma effects require TLR9-dependent NK cell activation. J Clin Invest. 2016 Jan;126(1):207-19. PubMed PMID: 26649979; PubMed Central PMCID: PMC4701545.
2. Brennan TV, Lin L, Huang X, Cardona DM, Li Z, Dredge K, Chao NJ, Yang Y. Heparan sulfate, an endogenous TLR4 agonist, promotes acute GVHD after allogeneic stem cell transplantation. Blood. 2012 Oct 4;120(14):2899-908. PubMed PMID: 22760779; PubMed Central PMCID: PMC3466971.
3. Brennan TV, Jaigirdar A, Hoang V, Hayden T, Liu FC, Zaid H, Chang CK, Bucy RP, Tang Q, Kang SM. Preferential priming of alloreactive T cells with indirect reactivity. Am J Transplant. 2009 Apr;9(4):709-18. PubMed PMID: 19344462. NIH Public Access Policy does not apply.
4. Xavier R, Brennan T, Li Q, McCormack C, Seed B. Membrane compartmentation is required for efficient T cell activation. Immunity. 1998 Jun;8(6):723-32. PubMed PMID: 9655486. NIH Public Access Policy does not apply.

B. Positions and Honors

Positions and Employment

2009 - 2014	Assistant Professor of Surgery, Duke University Medical Center, Durham, NC
2014 -	Associate Professor of Surgery, Duke University Medical Center, Durham, NC

Other Experience and Professional Memberships

1992 -	Member, Phi Beta Kappa
1999 -	Member, Massachusetts Medical Society
1999 - 2014	Member, American Medical Association
2002 -	Member, American College of Surgeons
2004 - 2014	Member, American Society of Transplantation
2007 -	Member, American Society of Transplant Surgeons
2007 - 2013	Member, Howard C. Naffziger Surgical Society
2010 -	Member, Association for Academic Surgery
2010 - 2014	Member, American Association for the Study of Liver Disease
2011 -	Fellow (F.A.C.S), American College of Surgeons
2011 - 2013	Membership Committee, Association for Academic Surgery
2013 -	Member, Society of University Surgeons
2014 -	Executive Council, Association for Academic Surgery
2015 -	Nominating Committee, Association for Academic Surgery

Honors

1991	University of California Los Angeles, Geissman Award for Organic Chemistry
1992	University of California Los Angeles, Presidential Fellowship
1992	University of California Los Angeles, Dept of Chemistry & Biochemistry Research Award
1993	University of California Los Angeles Arthur Furst Award for Undergraduate Research
1994	University of California Los Angeles, Departmental Scholar
1994	University of California Los Angeles, Departmental Highest Honors
1994	University of California Los Angeles, Merck Index Award for Undergraduate Research
1994	Harvard Medical School, Medical Scientist Training Program Award
2003	American College of Surgeons, Resident Research Fellowship
2004	American Society of Transplant Surgeons, Roche Laboratories Scientist Scholarship
2004	University of California San Francisco, Most Outstanding Resident Research Award
2004	American Society of Transplant Surgeons, Young Investigator Award
2007	American Society of Transplant Surgeons, Novartis Fellowship in Transplantation
2010	American Society of Transplant Surgeons, Vanguard Award
2010	NIH/NIAID, Loan Repayment 2-yr Award
2010	American Society of Transplantation, Basic Science Faculty Development Grant
2010	American Association for the Study of Liver Disease, Career Development Award
2012	NIH/NIAID, Clinical Scientist Career Development Award (K08, 5-year Award)
2014	NIH/NIAID, Loan Repayment 2-yr Award
2015	Duke University Medical Center, Gardner Award for Basic Science Research
2016	Duke University Medical Center, Transplant Center Award
2016	Duke University Medical Center, Health Scholar Award

C. Contribution to Science

1. Produced a CD4+ T-cell receptor transgenic (TCR-tg) mouse with direct allospecificity against the I-Ad MHC class II molecule. I produced this mouse for the specific study of alloimmunity in the setting of transplantation. Using this mouse, along with CD4+ indirect TCR-tg mice, I was able to delineate the contributions of direct and indirect allospecificity in acute cardiac allograft rejection. I was also able to demonstrate the therapeutic potential of allospecific regulatory T cells (Tregs) in suppressing acute cardiac allograft rejection using Tregs isolated from this TCR-tg mouse.

a. Brennan TV, Hoang V, Garrod KR, Liu FC, Hayden T, Kim J, Kang SM. A new T-cell receptor transgenic model of the CD4+ direct pathway: level of priming determines acute versus chronic rejection. Transplantation. 2008 Jan 27;85(2):247-55. PubMed PMID: 18212630. NIH Public Access Policy does not apply.

b. Brennan TV, Jaigirdar A, Hoang V, Hayden T, Liu FC, Zaid H, Chang CK, Bucy RP, Tang Q, Kang SM. Preferential priming of alloreactive T cells with indirect reactivity. Am J Transplant. 2009 Apr;9(4):709-18. PubMed PMID: 19344462. NIH Public Access Policy does not apply.

c. Brennan TV, Tang Q, Liu FC, Hoang V, Bi M, Bluestone JA, Kang SM. Requirements for prolongation of allograft survival with regulatory T cell infusion in lymphosufficient hosts. J Surg Res. 2011 Jul;169(1):e69-75. PubMed PMID: 21571317; PubMed Central PMCID: PMC3114634.

2. Determined the role of an endogenous TLR agonist, heparan sulfate, in activating allospecific T cells and promoting graft-versus host disease (GvHD) in the setting of allogeneic hematopoietic stem cell transplantation (HSCT). Revealed that elevations in serum heparan sulfate levels correlates with the onset of GvHD in patients receiving allogeneic HSCT. Demonstrated the ability of alpha-1-antitrypsin to decrease serum heparan sulfate levels in the setting of allogeneic HSCT and to decrease GvHD severity. Determined role of a heparan sulfate mimetic for the activation of natural killer cells and demonstrated their increased efficiency in eliminating lymphoma.

   a. Brennan TV, Lin L, Brandstadter JD, Rendell VV, Dredge K, Huang X, Yang Y. Heparan sulfate mimetic PG545-mediated antilymphoma effects require TLR9-dependent NK cell activation. J Clin Invest. 2016 Jan;126(1):207-19. PubMed PMID: 26649979; PubMed Central PMCID: PMC4701545.

   b. Brennan TV, Rendell VR, Yang Y. Innate immune activation by tissue injury and cell death in the setting of hematopoietic stem cell transplantation. Front Immunol. 2015;6:101. PubMed PMID: 25852683; PubMed Central PMCID: PMC4360715.

   c. Brennan TV, Lin L, Huang X, Cardona DM, Li Z, Dredge K, Chao NJ, Yang Y. Heparan sulfate, an endogenous TLR4 agonist, promotes acute GVHD after allogeneic stem cell transplantation. Blood. 2012 Oct 4;120(14):2899-908. PubMed PMID: 22760779; PubMed Central PMCID: PMC3466971.

   d. Brennan TV, Lunsford KE, Kuo PC. Innate pathways of immune activation in transplantation. J Transplant. 2010;2010. PubMed PMID: 20871653; PubMed Central PMCID: PMC2939398.

3. Was the first to demonstrate that the cell membrane of the T cell was compartmentalized based on hydrophobic qualities of membrane components. Revealed that this compartmentalization was critical to T cell receptor signal transduction.

   a. Xavier R, Brennan T, Li Q, McCormack C, Seed B. Membrane compartmentation is required for efficient T cell activation. Immunity. 1998 Jun;8(6):723-32. PubMed PMID: 9655486. NIH Public Access Policy does not apply.

4. Defined mechanistic detail on the deamidation of asparagine residues and isomerization of aspartate residues in peptide in proteins. Specifically investigated contribution of solvent dielectric and adjacent residue effects. Demonstrated the ability of iso-aspartyl methyltransferase to repair protein damage resulting from spontaneous deamidation.

   a. Brennan TV, Clarke S. Spontaneous degradation of polypeptides at aspartyl and asparaginyl residues: effects of the solvent dielectric. Protein Sci. 1993 Mar;2(3):331-8. PubMed PMID: 8453372; PubMed Central PMCID: PMC2142383.

   b. Brennan TV, Clarke S. Mechanism of cleavage at Asn 148 during the maturation of jack bean concanavalin A. Biochem Biophys Res Commun. 1993 Jun 30;193(3):1031-7. PubMed PMID: 8323528. NIH Public Access Policy does not apply.

   c. Brennan TV, Anderson JW, Jia Z, Waygood EB, Clarke S. Repair of spontaneously deamidated HPr phosphocarrier protein catalyzed by the L-isoaspartate-(D-aspartate) O-methyltransferase. J Biol Chem. 1994 Oct 7;269(40):24586-95. PubMed PMID: 7929130. NIH Public Access Policy does not apply.

d. Brennan TV, Clarke S. Effect of adjacent histidine and cysteine residues on the spontaneous degradation of asparaginyl- and aspartyl-containing peptides. Int J Pept Protein Res. 1995 Jun;45(6):547-53. PubMed PMID: 7558585. NIH Public Access Policy does not apply.

D. Research Support

Ongoing Research Support

NIH/NIAID K08 AI101263 Brennan (PI) 07/01/2012-06/30/2017
Role of Endogenous Toll-Like Receptor Ligands in Allospecific T Cell Activation
The goal of this study is to identify endogenous mediators of inflammation and determine their contribution to transplant allograft rejection.
Role: PI

Health Scholar Award Brennan (PI) 12/15/2016-11/01/2020
Duke University Medical Center
The goal of this award is to determine inflammatory properties and molecular pathways involved in mitochondrial injury in transplant allografts related to ischemia-reperfusion injury, and to develop methods to mitigate this injury.
Role: PI

Clarence Gardner Award Brennan (PI) 06/01/2016-05/31/2017
Duke University Medical Center
The Role of Serum Inflammatory Factors in Deceased Organ Donors on Innate Activation.
The goal of this award is to identify circulating endogenous damage associated factors in deceased organ donors with the goal of developing methods to prevent their accumulation or block their activity.
Role: PI

Transplant Center Award Brennan (PI) 07/01/2012-06/30/2017
Duke University Medical Center
The Role of Serum Inflammatory Factors in Deceased Organ Donors on Innate Activation
The goal of this award is to identify circulating endogenous damage associated factors in deceased organ donors with the goal of developing methods to prevent their accumulation or block their activity.
Role: PI

Completed Research Support

L30 AI090991-02 Brennan (PI) 07/01/2013-06/30/2015
Role of Endogenous Toll-Like Receptor Ligands in Allospecific T Cell Activation
This is a loan repayment program for clinical scientists sponsored by the NIH.
Role: PI

Basic Scientist Award Brennan (PI) 07/01/2010-06/30/2012
American Society of Transplantation.
Role of the innate immune system in the activation of allospecific T cells
The goal of this study is to identify endogenous mediators of inflammation and determine their contribution to transplant allograft rejection.
Role: PI

Career Development Award Brennan (PI) 07/01/2010-06/30/2012
American Association for the Study of Liver Disease.
Role of the innate immune system in the activation of allospecific T cells
The goal of this study is to identify endogenous mediators of inflammation and determine their contribution to transplant allograft rejection.
Role: PI

Hartwell Foundation Markert (PI) 05/01/2012-04/30/2015
Use of Thymus Transplantation to Induce Tolerance to Liver Transplants Transplant Rejection

The goal of this study is to determine if co-transplantation of thymus would induce central immune tolerance to liver allografts in rats.
Role: Co-investigator

Biomarker Foundation Brennan (PI) 07/01/2013-06/30/2015
Heparan Sulfate as a Serum Biomarker for Kidney Transplant Rejection
The role of this study is to determine the relevance of heparan sulfate as a serum biomarker of acute renal allograft rejection.
Role: PI

Pfizer Study 1252 Brennan (PI) 07/01/2013-06/30/2015
A Phase 1, Open Label Study to Evaluate the Effect of Tofacitinib (CP-690,550) Administration and Withdrawal on Immune Cell Function in Healthy Volunteers
My role in this study was to determine the effect of the Tofacitinib on human neutrophil function.
Role: PI on Multiple-PI grant