

BIOGRAPHICAL SKETCH

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NAME: Todd Victor Brennan

eRA COMMONS USER NAME (agency login): TODDBRENNAN

POSITION TITLE: 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 and laboratory training in biochemistry, molecular biology and immunology. I also have extensive 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, such as heparan sulfate (1,2) and mitochondria (3,4). I seek to better understand how these molecules activate the adaptive immune system and promote organ dysfunction and rejection. Defining key mediators of the inflammatory response will highlight mechanisms that can be targeted therapeutically to improve graft function and survival.

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.
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.
3. Pollara J, Edwards RW, Lin L, Bendersky VA, **Brennan TV**. Circulating mitochondria in deceased organ donors are associated with immune activation and early graft dysfunction. JCI Insight. 2018 Aug 9;3(15). PMID: 30089724.
4. Lin L, Xu H, Bishawi M, Feng F, Samy K, Truskey G, Barbas AS, Kirk AD, **Brennan TV**. Circulating mitochondria in organ donors promote allograft rejection. Am J Transplant. 2019 Jul;19(7):1917-1929. PMID: 30761731.

B. Positions and Honors

Positions and Employment

2009 - 2014 Assistant Professor of Surgery, Duke University Medical Center, Durham, NC
2014 - 2018 Associate Professor of Surgery, Duke University Medical Center, Durham, NC
2018 - 2020 Associate Professor of Surgery, Cedars-Sinai Medical Center, Los Angeles, CA
2020 - present Professor of Surgery, Cedars-Sinai Medical Center, Los Angeles, CA

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 - 2018 Nominating Committee, Association for Academic Surgery
2017 - Member, American Association of Immunology
2017 - 2020 Publications Committee, Society of University Surgeons
2017 - 2020 Cell Transplant Committee, American Society of Transplant Surgeons
2018 - National Kidney Foundation Board Member, Southern California

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. Demonstrated that circulating mitochondria in deceased organ donors are internalized by allograft endothelial cells and dendritic cells, leading to their activation, and predisposing allografts to dysfunction and rejection. Demonstrated that different pathways of cell death release mitochondria with distinct inflammatory properties.
 - a. Pollara J, Edwards RW, Lin L, Bendersky VA, **Brennan TV**. Circulating mitochondria in deceased organ donors are associated with immune activation and early graft dysfunction. JCI Insight. 2018 Aug 9;3(15). PMID: 30089724; PMCID: PMC6129133.
 - b. Lin L, Xu H, Bishawi M, Feng F, Samy K, Truskey G, Barbas AS, Kirk AD, **Brennan TV**. Circulating mitochondria in organ donors promote allograft rejection. Am J Transplant. 2019 Jul;19(7):1917-1929. PMID: 30761731; PMCID: PMC6591073
 - c. Zhu M, Barbas AS, Lin L, Scheuermann U, Bishawi M, **Brennan TV**. Mitochondria released by apoptotic cell death initiate innate immune responses. Immunohorizons. 2018 Dec;2(11):384-397. PMID: 30847435; PMCID: PMC6400482.
 - d. Nash AL, Samoylova M, Zhu M, Lin L, Leuthner T, Meyer JN, **Brennan TV**. Effects of Immunosuppressive Medications on Mitochondrial Function. J Surg Res. 2020 Jan 6;249:50-57. doi: 10.1016/j.jss.2019.12.010. PMID: 31918330.
2. Developed a novel CD4+ T-cell receptor transgenic mouse model with direct allospecificity for the study of solid organ and hematopoietic stem cell transplantation mechanisms. Used this model to demonstrate the contribution of direct and indirect presentation on allograft rejection.
 - 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. 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. 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. PMID: 21571317; PMCID: PMC3114634.
 - d. Chung J, Radojic V, Perkey E, Parnell T, Niknafs Y, Jin X, Friedman A, Labrecque N, Blazar BR, **Brennan TV**, Siebel CW, Maillard I. Early Notch signals induce a pathogenic molecular signature during priming of alloantigen-specific conventional CD4+ T cells in graft-versus-host disease. J Immunol. 2019 Jul 15;203(2):557-568. doi: 10.4049/jimmunol. PMID: 31182480
3. Described how the extracellular matrix polysaccharide, heparan sulfate, is an endogenous TLR4 agonist that activates allospecific T cells and promotes graft-versus host disease in the setting of allogeneic hematopoietic stem cell transplantation. Discovered the mechanism by which heparan sulfate mimetics can activate natural killer cells for the purpose of eliminating lymphoma.
 - a. **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. PMID: 25852683; PMCID: PMC4360715.
 - b. **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. PMID: 22760779; PMCID: PMC3466971.
 - c. Barbas AS, Lin L, McRae M, MacDonald AL, Truong T, Yang Y, **Brennan TV**. Heparan sulfate is a plasma biomarker of acute cellular allograft rejection. PLoS One. 2018 Aug 7;13(8). PMID: 30086133; PMCID: PMC6080752.
 - d. **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. PMID: 26649979; PMCID: PMC4701545.

4. Described the mechanism of spontaneous deamidation of asparagine residues in proteins, and how it results in the production of aspartate and iso-aspartate residues. Demonstrated how iso-aspartyl methyltransferase repairs protein damage resulting from iso-aspartyl formation.
 - 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

Department of Surgery Award
Cedars-Sinai Medical Center

Brennan (PI)

07/01/2018-06/30/2021

The Role of Circulating Mitochondria in Deceased Organ Donors on Innate Immune 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 for the purpose of improving transplant graft function and survival.

Role: PI

Completed 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)

12/15/2016-06/01/2018

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

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		