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 as 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, particularly mitochondria. I seek to better understand how these molecules activate the adaptive immune system and promote organ dysfunction and rejection (3,4). Defining key mediators of the inflammatory response to tissue injury 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; 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 - 2018	Associate Professor of Surgery, Duke University Medical Center, Durham, NC
2018 - present	Associate 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 -	Advisor for the National Kidney Foundation

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 [Available on 2020-07-01]
    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. Lubkin D, Bishawi M, Barbas A, Brennan TV, Kirk AD. Extracellular Mitochondrial DNA and N-Formyl Peptides in Trauma and Critical Illness: A Systematic Review. Crit Care Med. 2018 Dec;46(12):2018-2028. PMID: 30113320. NIH Public Access Policy does not apply.

2. Described the relative contributions of the direct and indirect pathways of alloantigen recognition in the setting of acute allograft rejection. Demonstrate the therapeutic potential of regulatory T cells with direct allo-specificity in suppressing acute graft 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.

3. Described how heparan sulfate, an endogenous TLR4 agonist, activates allospecific T cells and promotes graft-versus host disease (GvHD) in the setting of allogeneic hematopoietic stem cell transplantation (HSCT). Found that elevated heparan sulfate levels in patient serum correlate with GvHD following HSCT and allograft rejection following kidney transplant. Discovered the mechanism by which heparan sulfate mimetics can activate natural killer cells for the purpose of 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. PMID: 26649979; 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. PMID: 25852683; 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. PMID: 22760779; PMCID: PMC3466971.
    d. 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.

4. Described the mechanism of spontaneous deamidation of asparagine residues in proteins, which results in the production of abnormal iso-aspartate residues. Demonstrated how an iso-aspartyl methyltransferase can repair 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 — Brennan (PI) — 07/01/2018-06/30/2021
Cedars-Sinai Medical Center
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