BIOGRAPHICAL SKETCH

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NAME:Lloyd Kasper

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

POSITION TITLE:Professor Microbiology/Immunology and Medicine

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
University of Illinois Champaign-Urbana	BS	1970	Zoology
University of Illinois Champaign_Urbana	MS	1974	Zoology
Dartmouth College	MS (HON)	1992	
Rush University-Chicago	MD	1975	

A. Personal Statement

My lab has been focused on the role of the gut microbiome in CNS demyelinating disease for over a decade. During this period of time we have established a number of important parameters including the capacity of oral antibiotics to induce resistance to disease susceptibility, the role of regulatory T and B cells in this process and the identification of novel pathways activated by this immune regulatory process. In the past 8 years, we have focused on the capacity of certain gut commensal bacteria in the induction of immune protection against EAE, the experimental model of human multiple sclerosis and the mechanism by which these gut flora can enhance immune regulation. We have focused on the commensal symbiont, *Bacteroides fragilis,* in this process Over the past several years we have extended our work to investigate the mechanism by which several FDA approved therapeutics used in the treatment of relapsing MS alter the gut associated lymphoid tissue and perhaps the gut microflora themselves giving rise to a population of gut specific regulatory T and B cells.

B. Positions and Honors

1975-1979 Intern in Internal Medicine, Resident and Chief Resident in Neurology, DHMC, Hanover NH
1979-1987 Instructor/Assistant Professor in Medicine and Microbiology, Dartmouth Medical School
1987-1993 Associate Professor, Departments of Medicine and Microbiology/Immunology
1993-present Professor, Department of Microbiology.Immunology and Medicine
1998-2011 Director, Multiple Sclerosis Center at Dartmouth
2005-2011 Co-Director Dartmouth Program in Immunotherapeutics

- NIH Clinical Investigator Award, 1983
- NIH Young Scientist Award, 1983
- American Association of Immunologists, 1985
- NIH Research Career Development Award, 1989
- AIDS and Related Disorders Study Section E, NIH, 1994
- Fogarty Senior International Fellowship, 1996
- Trop. Med and Parasitology Study Section, NIH, 1990-94
- Chairman, NIH AIDS Related Study Section E, 1996-2000
- Organizer, Keystone Symposia on Opportunistic Infections in AIDS, 1998

- Organizer, Keystone Symposia on Translational Medicine in Autoimmunity, 2005
- Advisory Committee on Fellowships, National MS Society 2004-present
- Organizer, Annual Dartmouth Life Science Symposia on Autoimmunity 2006-present
- Co-organizer, Dartmouth/University of Vermont Northern New England Symposia on Neuroimmunology 2002, 2004, 2006, 2007, 2010
- Member, NIH DSMB autologous stem cell transplantation in autoimmunity 2004-present
- Organizer, Keystone Symposia on Gut Microbiome: Effector/Regulatory Networks. Taos, NM 2013
- Stanley F. Waterman Lectureship for National MS Society Boston 2014

C. Contribution to Science

1. Mucosal immunity to the obligate intracellyular parasite, T. gondii

Buzoni-Gatel, D.B., Debbabi, H.J., Moretto, M., Dimier-Poisson, Lepage, A.C., Bout, D. and Kasper, L.H. Intraepithelial lympphocytes traffic to the intestine and enhance resistance to T. gondii oral infection. *Journal of Immunology* 162:5846-5852, 1999

Buzoni-Gatel, D.B., Debbabi, H.J., Moretto, M., Dimier-Poisson, Lepage, A.C., Bout, D. and Kasper, L.H. Intraepithelial lympphocytes traffic to the intestine and enhance resistance to T. gondii oral infection. *Journal of Immunology* 162:5846-5852, 1999

Buzoni-Gatel, D., Debbabi, H.., Mennechet, F.J., Martin, V., Lepage, A.C., Schwartzman, J.D., Kasper, L.H. Murine ileitis after intracellular parasite infection is controlled by TGF-beta-producing intraepithelial lymphocytes. *Gastroenterology* 120:914-24, 2001

Li, W., Buzoni-Gatel D., Debbabi H., Hu M.S., Mennechet F.J.D., Durell B.G., Noelle R.J., Kasper L.H. CD40/CD154 ligation is required for the development of acute ileitis following oral infection with an intracellular pathogen in mice *Gastroenterology,* 122:762-73, 2002

Mennechet F.J., Kasper L.H., Rachinel N., Li W., Vandewalle A., Buzoni-Gatel Lamina propria CD4(+) T lymphocytes synergize with murine intestinal epithelial cells to enhance proinflammatory response against an intracellular pathogen. *J Immunol*. 168:2988-96, 2002

2. *Isolation and characterization of P30, the major surface antigen of T. gondii*

Kasper, L.H., Crabb, J. and Pfefferkorn, E.R. Isolation and characterization of monoclonal antibody resistant antigen mutant of *Toxoplasma gondii*. *Journal of Immunology*, 129:1694-1699, 1982

Kasper, L.H., Crabb, J.H. and Pfefferkorn, E.R. Purification of a major membrane protein of *Toxoplasma gondii* by immunoabsorption with a monoclonal antibody. *Journal of Immunology*, 130:2407-2412, 1983

Kasper, L.H., Currie, K.M. and Bradley, M.S. An unexpected response to vaccination with a purified major membrane tachyzoite antigen (P30) of *Toxoplasma gondii*. *Journal of Immunology.* 134:3426-3431, 1985.

Joiner, K.A., Furhman, S.A., Kasper, L.H., Mellman I. Route of entry of *T.gondii* determines fusion competence of paracidophorous vacuoles in transfected CHO cells. *Science*, 249:597, 1990

3. *The critical impact of CD8+ T cells in host immunity to the obligate intracellular parasite, T. gondii*

Khan, I.A., Ely, K. and Kasper, L.H. A purified parasite antigen (P30) mediates CD8+ T cell immunity against fatal toxoplasma infection in mice. *Journal of Immunology* 147:3501, 1991

Bulow, R., Kasper, L.H. and Boothroyd, J.C. Protection of mice from fatal *T. gondii* infection by immunization with P30 antigen. *Journal of Immunology.* 147:3496, 1991

Kasper, L.H., Khan, I.A., Ely, K., Buelow, R. and Boothroyd, J. Antigen specific (P30) mouse CD8+ T cells are cytotoxic against *Toxoplasma gondii* infected peritoneal macrophages *Journal of Immunology*, 148:1493, 1992

Mineo, J.R., McLeod R. and Kasper, L.H. Antibodies to *T. gondii* major surface protein (P30) inhibit attachment to and invasion of host cells and are produced in murine intestine after peroral infection. *Journal of Immunology* 150:3951-3964, 1993

Khan, I.A., Ely, K.E. and Kasper, L.H. Protective immunity against acute and chronic murine toxoplasmosis by a P30 antigen-specific CD8+ T cell clone. *Journal of Immunology* 152:1856-1861, 1994

Khan, I.A., Matsuura, T. and Kasper, L.H. IL-12 mediates enhanced protection against acute toxoplasma infection. *Infection and Immunity* 62: 1639-1642, 1994

Luangsay S., Kasper L.H., Rachinel N., Minns L.A., Mennechet F.J., Vandewalle A., Buzoni-Gatel D. CCR5 mediates specific migration of Toxoplasma gondii-primed CD8 lymphocytes to inflammatory intestinal epithelial cells. *Gastroenterology* 125: 491-500, 2003

4. *The role of the gut microbiome in the control of CNS demyelinating disease*

Ochoa-Repáraz J., Mielcarz D.W., Ditrio L.E., Burroughs A.R., Foureau D.M., Haque-Begum S., Kasper L.H. Role of Gut Commensal Microflora in the Development of Experimental Autoimmune Encephalomyelitis. J Immunol. 2010 185(7):4101-8

Nowak E.C., Weaver C.T., Turner H., Begum-Haque S., Becher B., Schreiner B., Coyle A.J., Kasper L.H., Noelle R.J. IL-9 as a mediator of Th17-driven inflammatory disease. J Exp Med. 2009 206:1653-60.

Ochoa-Repáraz J., Mielcarz D.W., Begum-Haque S., Kasper L.H. Gut, bugs, and brain: role of commensal bacteria in the control of central nervous system disease. Ann Neurol. 2011 69:240-7

Begum-Haque S., Christy M., Ochoa-Reparaz J., Nowak E.C., Mielcarz D., Haque A., Kasper L.H. Augmentation of regulatory B cell activity in experimental allergic encephalomyelitis J Neuroimmunol. 2011. 232:136-4

5. *The capacity of Bacteroides fragilis and its isolated capsular polysaccharide antigen (PSA) to induce host immune regulation against CNS demyelinating disease*

Joscelyn J., Kasper L.H. Digesting the emerging role for the gut microbiome in central nervous system demyelination. Mult Scler. 2014 Jul 28

J. Ochoa-Repáraz, D.W. Mielcarz, Y. Wang, L. E. Ditrio, A. R. Burroughs, S. Haque-Begum, D.L. Kasper and L. H. Kasper. CNS demyelinating disease protection by the human commensal, Bacteroides fragilis, depends on Polysaccharide-A. J. Immunol. 2010. 185(7):4101-8

Wang Y., Telesford K.M., Ochoa-Repáraz J., Haque-Begum S., Christy M., Kasper E.J., Wang L., Wu Y., Robson S.C., Kasper D.L., Kasper L.H. An intestinal commensal symbiosis factor controls neuroinflammation via TLR2-mediated CD39 signalling. Nat Commun. 2014 Jul 21; 5:4432.

Telesford KM, Yan W, Ochoa-Reparaz J, Pant A, Kircher C, Christy MA, Begum-Haque S, Kasper DL, Kasper LH.A commensal symbiotic factor derived from Bacteroides fragilis promotes human CD39(+)Foxp3(+) T cells and Treg function. Gut Microbes. 2015 Jul 4;6(4):234-42

D. Research Support

Ongoing Research

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NAME OF PROFESSIONAL: Lloyd Kasper, M.D. Is this project active or pending? Active		
Project Number: AI110170 Name of Principal Investigator: Lloyd Kasper, M.D. Funding Source: Symbiotix Biotherapies, Inc. Title of Project *(or Subproject): Novel Commensal Polysaccharide Treats Multiple Sclerosis Through Treg Modulation*	Dates of Approved/Proposed Project: 06/01/15 – 09/30/17 Annual Direct Costs: $373,831	Percent Effort: 30%

What are the specific aims of this project?

Aim 1: Evaluate effect of PSA using human PBMC derived from patients with relapsing multiple sclerosis in an in vitro conversion assay.
Aim 2: Evaluate the clinical and immunological impact of oral PSA administration in a non-human primate experimental model of EAE.
Aim 3: Process development and manufacturing to produce cGMP material for clinical studies.

NAME OF PROFESSIONAL: Lloyd Kasper, M.D. Is this project active or pending? active		
Project Number: Name of Principal Investigator: Lloyd Kasper, M.D. Funding Source: Genzyme Corporation Title of Project *(or Subproject): Essential Role of CD39+Foxp3+ T regulatory cells in prevention of CNS demyelination in EAE mice following treatment with anti-muCD52 Ab*	Dates of Approved/Proposed Project: 04/01/2016-01/31/2018	Percent Effort: 10%

What are the specific aims of this project?

Aim 1: To determine whether CD39 and associated migratory molecules are essential for anti-CD52-mediated immune regulation during EAE.

Research support (past 3 years)

During the past three years, my lab has had extensive research support from the NIH, the National MS Society and industry. This has included the following:

NAME OF PROFESSIONAL: Lloyd Kasper, M.D. Is this project active or pending? completed		
Project Number: R56 Name of Principal Investigator: Lloyd Kasper, M.D. Funding Source: NIH Title of Project *(or Subproject): The role of gut microbiome in CNS demyelination*	Dates of Approved/Proposed Project: 07/01/13 – 06/30/14 Annual Direct Costs: $250,000	Percent Effort: 25%

What are the specific aims of this project?

To assess the capacity of a single antigen derived from B. fragilis in protection against EAE

NAME OF PROFESSIONAL: Lloyd Kasper, M.D. Is this project active or pending? Completed		
Project Number: Name of Principal Investigator: Lloyd Kasper, M.D. Funding Source: Symbiotix Biotherpaies STTR Phase I Title of Project *(or Subproject): Induction of T regulatory cells in EAE by the gut microbiome*	Dates of Approved/Proposed Project: 07/01/14 – 06/30/15 Annual Direct Costs: $164,147	Percent Effort: 25%

What are the specific aims of this project?

NIH Phase I STTR focused on the induction of regulatory T cells by a specific capsular polysaccharide derived from *B. fragilis*

NAME OF PROFESSIONAL: Lloyd Kasper, M.D. Is this project active or pending? completed		
Project Number: RG4662A2/1 Name of Principal Investigator: Lloyd Kasper, M.D. Funding Source: NMSS Title of Project *(or Subproject): Regulation of immunity by gut commensal bacteria in MS*	Dates of Approved/Proposed Project: 07/01/12 – 06/30/16 Annual Direct Costs: $164,147	Percent Effort: 27.5%

What are the specific aims of this project?

Aim 1: Polysaccharide A (PSA) derived from the human commensal *Bacteroides fragilis* is a symbiosis factor that stimulates immunologic development within mammalian hosts.

Aim 2: Identification of CD39+ T regs induced by PSA in EAE

NAME OF PROFESSIONAL: Lloyd Kasper, M.D.
Is this project active or pending? completed

Project Number: N/A Name of Principal Investigator: Lloyd Kasper, M.D. Funding Source: Teva Neuroscience Title of Project *(or Subproject):* Glatiramer acetate (GA) modulation of the gut-associated lymphoid tissue (GALT)	Dates of Approved/Proposed Project: 03/01/15 – 10/01/16 Annual Direct Costs: $140,008	Percent Effort: 10%

What are the specific aims of this project?

Aim 1: To identify the GALT-derived regulatory ymphocytes and the mucosal immune responsive APC populations following treatment with GA in EAE mice.

1a: Role of GALT derived DC in response to GA.
1b: Effect of GA treatment on GALT derived T_{reg} lymphocytes.
1c: Effect of GA treatment on GALT derived B_{reg} cells.

Aim 2: To identify the trafficking of APCs in particular $CD103^{+}$DC and B cells from the GALT to the CNS following GA treatment of EAE mice.

Aim 3 (optional depending on level of funding provided): To determine the effects of increased dose, less frequency of GA administration on the activation of GALT and peripheral regulatory populations in EAE mice

NAME OF PROFESSIONAL: Lloyd Kasper, M.D.
Is this project active or pending? completed

Project Number: N/A Name of Principal Investigator: Lloyd Kasper, M.D. Funding Source: Genzyme Corporation Title of Project *(or Subproject): Teriflunomide mediated gut-associated immune responses in EAE*	Dates of Approved/Proposed Project: 08/01/14 – 07/31/16	Percent Effort: 22.5%

What are the specific aims of this project?