BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: WEINER, Howard L. M.D.

eRA COMMONS USER NAME (credential, e.g., agency login): HLW123

POSITION TITLE: Robert L. Kroc Professor of Neurology

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
Dartmouth College, Hanover NH	B.A.	06/1965	Philosophy
University of Colorado School of Medicine	M.D.	06/1969	Medicine

A. Personal Statement

My background is in the field of neurology and immunology. My laboratory has had a long-term interest in the immunologic aspects of MS and the use of the mucosal immune system to treat autoimmune and other diseases. My laboratory interests include: immunoregulation in the EAE model of MS, mucosal immunology, microglia and immune mechanisms in other neurological diseases such as Alzheimer's disease and ALS. I have a specific interest in the microbiome and how it effects immune mediated and neurologic diseases. This interest stems from my long-term studies of oral tolerance. Presently, my laboratory is exploring novel mechanisms by which the microbiome can be modulated for the treatment of MS and we have carried out an immunologically based pilot trial of probiotics in MS.

B. Positions and Honors

Positions and Employment

1971-1974 Residency, Longwood Neurology Program Clinical Fellow, Harvard Medical School
1972-1974 Research Fellow, Massachusetts General Hospital
1974-1976 Research Fellow, Immunology, University of Colorado Medical Center, Denver, Colorado
1976-1977 Instructor in Neurology, Harvard Medical School
1977-1980 Assistant Professor of Neurology, Harvard Medical School
1980-1985 Associate Professor of Neurology, Harvard Medical School
1980 Director, Multiple Sclerosis Clinical and Research Unit, Brigham and Women's Hospital
1985 Co-Director, Center for Neurologic Diseases, Brigham and Women's Hospital
1985-1997 Robert L. Kroc Associate Professor of Neurologic Diseases, Harvard Medical School
1997 Robert L. Kroc Professor of Neurologic Diseases, Harvard Medical School
1998 Director, Partners Multiple Sclerosis Center, Brigham and Women's Hospital and Massachusetts General Hospital

Honors and Awards

1974-1976 Special Research Fellowship, Colorado Multiple Sclerosis Society
1976-1977 NIH Special Fellowship
1977-1982 Teacher Investigator Award, NINCDS
1985 Recipient of Robert L. Kroc Chair in Neurology for Multiple Sclerosis Research, Awarded by Kroc Foundation, Santa Inez, California
1988-1995 Javits Neuroscience Investigator Award, NINCDS
2004 Establishment of the Howard L. Weiner Professor of Neurology Endowed Chair, Harvard Medical School
2007 John Dystel Prize for Multiple Sclerosis Research, American Academy of Neurology
2008 Betty and David Koetser Memorial Prize

2009 Award for Outstanding Research Achievement, Nature Biotechnology SciCafé, Nature Publications

Major Committee Assignments

1976- Scientific Advisory Board, Massachusetts Multiple Sclerosis Society
1980-1983 Ad Hoc Member, Clinical Research Center Review Study Section, NIH
1982-1987 National Multiple Sclerosis Society Scientific Advisory Board, Committee on Research on the Etiology, Diagnosis, Natural History, Prevention and Therapy of Multiple Sclerosis
1982- National Multiple Sclerosis Society Committee on Working Trials of New Drugs in MS
1983-1988 New Pathways Project, Harvard Medical School
2004 MS Board

Clinical and Hospital Service Responsibilities

1980-1997 Director, Multiple Sclerosis inpatient/outpatient clinical services, Brigham & Women's Hospital, Boston, MA
1985- Co-Director, Center for Neurologic Diseases, Brigham and Women's Hospital
1998- Director, Multiple Sclerosis Center, Brigham & Women's and Massachusetts General Hospitals

Licensure and Board Certification:

1978 American Board of Psychiatry and Neurology

C. Contributions to Science

1. **Immune Mechanisms in Multiple Sclerosis.** Multiple sclerosis has long been considered an immune mediated disease, but the mechanisms of immune dysregulation and function are not completely understood. I have studied immune mechanisms in MS, including the identification of regulatory T cell function, the presence of activated T-cells, immune function related to response to therapy I have investigated new mechanisms of immune dysregulation including the use of antigen arrays in micro-RNAs. These findings have helped provide the basis for understanding MS, monitoring response to treatment and development of new therapies.
   a. Murugaiyan G, da Cunha AP, Ajay AK, Joller N, Garo LP, Kumaradevan S, Yosef N, Vaidya VS, Weiner HL. MicroRNA-21 promotes Th17 differentiation and mediates experimental autoimmune encephalomyelitis. J Clin Invest. 2015 Feb 2. pii: 74347. PMCID: PMC4362225
   b. Quintana FJ, Farez MF, Viglietta V, Iglesias AH, Merbl Y, Izquierdo G, Lucas M, Basso AS, Khoury SJ, Lucchinetti CF, Cohen IR, Weiner HL. Antigen microarrays identify unique serum autoantibody signatures in clinical and pathologic subtypes of multiple sclerosis. Proc Natl Acad Sci U S A. 105(48):18889-94, 2008. PMCID: PMC2596207
   c. Gandhi R, Healy B, Gholipour T, Egorova S, Musallam A, Shuja M, Nejad P, Patel B, Hei H, Khoury S, Quintana F, Kivisakk P, Chitnis T, Weiner HL. Circulating microRNAs as biomarkers for disease staging in multiple sclerosis. Ann Neurol. 73(6):729-40, 2013. Not federally funded.
   d. Murugaiyan G, Mittal A, Lopez-Diego R, Maier LM, Anderson DE, Weiner HL. IL-27 Is a Key Regulator of IL-10 and IL-17 Production by Human CD4+ T Cells. J Immunol. 183(4):2435-43, 2009. PMCID: PMC2904948

2. **Clinical MS Studies, including the CLIMB Observational Cohort Study.** I have been at the forefront of clinical studies in MS, including clinical trials, such as the use of cyclophosphamide, plasma exchange, monoclonal antibodies and antigen tolerance. These studies have led to the use of new therapeutic approaches in MS that have been integrated into common clinical practice. In addition, I have established the CLIMB observational cohort study in 2000, which is part of a comprehensive MS Center, in which patients are tracked with yearly MRI, clinical evaluation and blood studies. This one of a kind observational study has served as a model for the investigation of MS and the establishment of a comprehensive MS Center has been replicated throughout the United States and overseas based on the model we established at the Brigham and Women's Hospital.
   a. Gauthier SA, Glanz BI, Mandel M, Weiner HL. A model for the comprehensive investigation of a chronic autoimmune disease: the multiple sclerosis CLIMB study. *Autoimmun Rev*. 5(8):532-6, 2006. Not federally funded.
   b. Gauthier SA, Mandel M, Guttmann CRG, Glanz BI, Khoury SJ, Betensky RA, Weiner HL. Predicting short-term disability in multiple sclerosis. *Neurology*. 68(24):2059-65, 2007. Not federally funded.
   c. Tauhid S, Mohit N, Healy B, Weiner HL and Bakshi R. MRI phenotypes based on cerebral lesions and atrophy in patients with multiple sclerosis. *Neurol Sci*. 346(1-2):250-4, 2014. Not federally funded.

d. Rotstein DL, Healy BC, Malik MT, Chitnis T, Weiner HL. Evaluation of no evidence of disease activity in a 7-year longitudinal multiple sclerosis cohort. *JAMA Neurol*. 2015 Feb 1;72(2):152-8. Not federally funded.

3. Mucosal Immunology and the Microbiome. by which the immune system induces tolerance is not well understood. I have pioneered the use of oral and nasal tolerance to understand regulatory T cells and as a method for treatment of autoimmune and inflammatory diseases. My studies on the gut associated lymphoid tissue have helped identify the gut and the gut microbiome as a crucial part of the immune system. As part of these studies, I have identified and characterized regulatory T cells, including a TGFbeta secreting Th3 cell that expresses LAP on its surface.
   a. Ochi H, Abraham M, Ishikawa H, Frenkel D, Yang K, Basso A, Wu H, Chen ML, Gandhi R, Miller A, Maron R, Weiner HL. New immunosuppressive approaches: Oral administration of CD3-specific antibody to treat autoimmunity. *J Neurol Sci*. 274(1-2):9-12, 2008. PMCID: PMC3167084.
   b. Wu HY, Maron R, Tukpah AM, Weiner HL. Mucosal anti-CD3 monoclonal antibody attenuates collagen-induced arthritis that is associated with induction of LAP+ regulatory T cells and is enhanced by administration of an emulsome-based Th2-skewing adjuvant. *J Immunol*. 185(6):3401-7, 2010. PMCID: PMC2962584.
   c. Gandhi R, Farez MF, Wang Y, Kozoriz D, Quintana FJ, Weiner HL. Cutting Edge: Human Latency-Associated Peptide+ T Cells: A Novel Regulatory T Cell Subset. *J Immunol*. 184(9):4620-4, 2010. PMCID: PMC2904991.
   d. Ilan Y, Maron R, Tukpah AM, Maioli TU, Murugaiyan G, Yang K, Wu HY, Weiner HL. Induction of regulatory T cells decreases adipose inflammation and alleviates insulin resistance in ob/ob mice. *Proc Natl Acad Sci U S A*. 107(21):9765-70, 2010. PMCID: PMC2906892.

4. Immune Mechanisms in Neurologic Diseases. I have used my expertise in immunology to investigate immune mechanisms in other neurologic diseases. This has included the study of Alzheimer's disease, in which I have measured reactivity to A-beta, have shown that immunotherapy using a proteasome adjuvant can clear A-beta in animal models, and that nasal administration of A-beta peptide is effective in animal models. These studies have provided the basis for better understanding immune mechanisms in Alzheimer's and the basis for immunotherapy. In amyotrophic lateral sclerosis, I have identified immune abnormalities in the animal model and in human disease, including abnormalities of microglial cells and peripheral monocytes. These studies were based on basic observations of the understanding and characterization of microglial cells in the brain. These findings now serve as a basis for clinical trials for the treatment of ALS. I am also investigating immune mechanisms other neurologic diseases including stroke and brain tumors.
   a. Frenkel D, Maron R, Burt DS, Weiner HL. Nasal vaccination with a proteosome-based adjuvant and glatiramer acetate clears beta-amyloid in a mouse model of Alzheimer disease. *J Clin Invest*. 115(9):2423-2433, 2005. PMCID: PMC1184038.
   b. Frenkel D, Puckett L, Petrovic S, Xia W, Chen G, Vega J, Dembinsky-Vaknin A, Shen J, Plante M, Burt DS, Weiner HL. A nasal proteosome adjuvant activates microglia and prevents amyloid deposition. *Ann Neurol*. 2008 May;63(5):591-601. PMCID:18460829.
   c. Butovsky O, Jedrychowski MP, Moore CS, Cialic R, Lanser AJ, Gabriely G, Koeglsperger T, Dake B, Wu PM, Doykan CE, Fanek Z, Liu L, Chen Z, Rothstein JD, Ransohoff RM, Gygi SP, Antel JP, Weiner HL. Identification of a unique TGF-β-dependent molecular and functional signature in microglia. *Nat Neurosci*. 17(1):131-43, 2014. PMCID: PMC4066672.
   d. Butovsky O, Jedrychowski M, Cialic R, Krasemann S, Murugaiyan G, Fanek Z, Greco D, Wu P, Doykan C, Kiner O, Lawson R, Frosch M, Pochet N, Fatimy R, Krichevsky A, Gygi S, Lassmann H, Berry J, Cudkowicz M, Weiner HL. Targeting miR-155 restores abnormal microglia and attenuates disease in SOD1 mice. *Ann Neurol*. 77(1):75-99, 2015. PMCID: PMC4432483.

Complete List of Published Work in My Bibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/howard.weiner.1/bibliography/40337048/public/?sort=date&direction=ascending

D. Additional Information: Research Support and/or Scholastic Performance

ACTIVE:

RR 2005-A-13 (Weiner, PI) 10/01/10 – 09/30/19
National Multiple Sclerosis Society
Risk Factors for Progression in MS
The goal of this project to determine degree therapies affect progression, heterogeneity, factors associated with different rates of progression in MS in a cross-center study involving four major academic MS centers. In a prospective pilot study that combines cohorts from each center, collect uniform data (clinical, MRI, blood, and genetics) on 1500 MS patients over the two-year period of the pilot grant. We will test hypotheses to determine which factors (eg, MRI, blood biomarkers) or combination of factors link to disease progression using data obtained during the two-year prospective data collection period and obtained on the cohort in the 5 years prior to this two-year period. Role: PI

CTA (Exhibit A1) (Weiner, PI) 09/29/15 – 09/28/18
Google Life Sciences LLC
SysteMS: A Systems Biology Study of Clinical, Radiological, and Molecular Markers in Subjects with Multiple Sclerosis
This is a longitudinal, clinical, radiological and biomarker study of subjects with MS. The goals are to gather data from clinical assessments, MRI, and molecular assays to perform multidimensional analysis of the datasets using a platform of analytic methods developed by GLS to identify factors associated with disease severity and progression in MS. Role: PI

R01 NS087226 (Weiner, PI) 09/30/14 – 07/31/19
NIH/NINDS
Gut Microbiota in Patients with Multiple Sclerosis
In this research proposal we hypothesize that changes in the gut microbiome are linked to susceptibility and immune changes that occur in MS as well as response to treatment. Role: PI

NMSS RG (Weiner, PI) 04/01/16 – 03/31/19
NMSS
Investigation of Pathogenic Gene Signature of Human TH17 cells in Multiple Sclerosis
The purpose of this study is to provide new insights in defining the role of TH17 cells in the pathogenesis of MS, help to identify a biomarker of TH17 cells in association of MS and help to identify gene targets for developing new MS treatment. Role: PI

R01EY027921 (Weiner, Butovsky: CO-PI) 09/01/17 – 08/31/20
NIH/NEI
Role of Microglia in Retinitis Pigmentosa
The focus of this grant proposal is to characterize retinal microglia and how they regulate and/or participate in retinal damage in both animal models of retinitis pigmentosa and in eyes from human subjects. We will investigate whether retinitis pigmentosa in animal models can be treated by specifically targeting and modulating microglia. We will use new technology and approaches to understand features of microglia cells that can then be exploited to develop novel microglia-targeting therapies to treat humans with retinitis pigmentosa. Role: Co-PI

Research Grant (Weiner, Liu Co-PI) 04/01/18 – 03/31/21
NMSS
The Role of Fecal MicroRNAs in CNS Autoimmune Inflammatory Disease
Our hypothesis is the dynamic changes in fecal microRNAs during the course of EAE and in MS relate to immune mechanisms associated with modulating disease.
Aim 1: Investigation of fecal microRNAs in EAE; Aim 2: Effect of protective fecal microRNAs on the microbiome and immune mechanisms in EAE; Aim 3: Effect of synthetic microRNAs on immune function and the microbiome in EAE. Role: PI

COMPLETED**:**

A203325.03 (Weiner, PI) 12/01/09 – 06/30/18
EMD Serono, Inc.
CLIMB Study
The purpose of this study is to identify clinical and MRI features in MS patients followed longitudinally that characterize disease subtypes, prognosis and response to therapy. Role: PI

P01 NS076410 (Weiner, PD/PI) 12/01/12 – 11/30/17
NIH/NINDS
Transcriptional Control of Autoimmunity in the Central Nervous System
Project 4 *- Molecular Analysis of Effector and Regulatory T Cell Responses in MS*
Core A
Summary: The primary goal of this program project grant (PPG) is to identify molecular mechanisms of how IL-27 inhibits effector T cells and induces regulatory Tr1 cells with a focus on two transcription factors cMaf and AhR, both of which are induced by IL-27 in responding Tr1 cells. The investigation of the inter-relationship of cytokines and transcription factors in both animal models and MS patients will allow a better basic understanding of immune abnormalities in MS and allow both the development of more specific immunomodulatory therapy and a mechanistic understanding of current therapies being used to treat MS. IFNβ, a widely used first line therapy in MS has been shown to act in part by the induction of IL-27, underscoring the importance of studying this pathway in CNS autoimmunity.
Project 4 investigates the synergistic effect of IL-27 and AhR activation in both adaptive and innate immune responses in human subjects and in patients with multiple sclerosis. We will investigate how IL-27 and AhR crosstalk at the molecular level. IFNβ, a widely used first line therapy in MS has been shown to act in part by the induction of IL-27, underscoring the importance of studying this pathway in CNS autoimmunity. Role: P
The Administrative Core is responsible for providing scientific administration and coordination, fiscal oversight and administrative support for this program project, keeping the Program a highly integrative and interactive consortium. Role: PI

M-Baranzini-BWH-01sc (Sub PI: Weiner/Chitnis) 10/01/15 – 09/30/17
Regents of the University of California
International MS Microbiome Study
The objective of this study is to (1) identify and characterize the communities of gut microbes, characteristic of subjects with MS and (2) to investigate the extent to which variation in an individual's DNA sequence can affect the populations of bacteria that colonize his/her gut. Role: Co-PI

2016D006139 (Weiner, PI) 08/01/16 – 07/31/17
Partners Healthcare Innovation
Anti-LAP Antibody: A New Checkpoint Inhibitor for the Treatment of Cancer
We are developing a first in class biologic agent for the treatment of cancer that will functionally down-regulate and/or directly deplete Tregs in cancer patients. Our studies will identify and characterize anti-LAP antibodies for their transition into clinical studies. Anti-LAP treatment, alone or in combination with other modalities, has the potential to provide a novel checkpoint inhibitor and to control tumor growth. Role: PI

R01 AI043458 (Weiner, PI) 06/01/98 – 03/31/17
NIH/NINDS
Mechanisms of the Induction of Oral Tolerance
In this proposal, we will investigate the role that AHR plays in the induction of oral tolerance directly by promoting the differentiation of FoxP3+ Treg and IL10+ Tr1 cells, and indirectly both by interfering with the generation of effector T cells and by generating tolerogenic dendritic cells that promote Treg differentiation. In addition, we will investigate the use of AHR ligands as immunomodulators to enhance the induction of antigen specific oral tolerance. Role: PI