BIOGRAPHICAL SKETCH

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NAME: Raymond A. Sobel

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

POSITION TITLE: Professor of Pathology

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
Stanford University, Stanford, CA	B.S.	1972	Chemistry and Biology
University of California, San Francisco	M.D.	1976	Medicine

A. Personal Statement

I am a Board Certified and practicing neuropathologist with more than 35 years of experience in the neuropathologic and immunopathologic analysis of CNS tissues of multiple sclerosis patients, and animals with experimental autoimmune encephalomyelitis (EAE), and other inflammatory disease models. I have worked continuously in this field since 1981, and have collaborated on EAE and MS neuropathology studies with numerous investigators over many years. The following publications from 2016 on the pathology and immunopathology of EAE are relevant to this project:

1. Lehmann-Horn K, Sagan SA, Winger RC, Bernard CCA, **Sobel RA**, Zamvil SS. CNS accumulation of regulatory B cells is VLA-4-dependent. *Neurol Neuroimmunol Neuroinflam* 2016;3(2): e212doi: 10.1212/NXI.0000000000000212. PMID: 27027096. PMCID: PMC4794810.
2. Schulze-Topphoff U, Varrin-Doyer M, Pekarek K, Shetty S, Sagan SA, Spencer CM, **Sobel RA**, Wipke B, Steinman L, Scannevin RH, Zamvil SS. Dimethyl fumarate treatment can induce adaptive and innate immune modulation independent of Nrf2. *Proc Natl Acad Sci USA* 2016;113:4777-82 PMID: 27078105. PMCID: PMC4855599.
3. Varrin-Doyer M, Pekarek K, Spencer CM, Bernard CCA, **Sobel RA**, Cree BAC, Schulze-Topphoff1 U, Zamvil SS. Treatment of spontaneous EAE with laquinimod inhibits Tfh, reduces meningeal B cell aggregates and prevents disability progression. *Neurol Neuroimmunol Neuroinflam* 2016, 3:e272. PMID: 27704036.
4. Sagan SA, Winger RC, Cruz-Herranz A, Nelson PA, Hagberg S, Miller CN, Spencer CM, Ho PP, Bennett JL, Levy M, Levin MH, Verkman AS, Green AJ, Steinman L, Anderson MS, **Sobel RA**, Zamvil SS. Tolerance checkpoint bypass permits emergence of pathogenic T cells to neuromyelitis optica autoantigen aquaporin-4. *Proc Natl Acad Sci USA* 2016, www.pnas.org/cgi/doi/10.1073/pnas.1617859114. PMID: 27940915. PMCID: PMC5187685.

B. Positions and Honors

1976 – 1977 Intern in Pathology, University of California, Davis, CA
1977 – 1979 Resident in Anatomic Pathology, University of California, San Francisco, CA
1979 – 1980 Fellow in Neuropathology, University of California, Davis, CA
1980 – 1981 Fellow in Neuropathology, Stanford University and Palo Alto VA Medical Centers, Palo Alto, CA
1981 – 1984 Research Fellow in Immunopathology, Massachusetts General Hospital, Harvard Medical School, Boston, MA
1983 – 1984 Instructor in Pathology, Harvard Medical School, Boston, MA
1984 – 1989 Assistant Professor, Neuropathology, Pathology, Harvard Medical School, Massachusetts General Hospital, Boston, MA
1990 – 1992 Associate Professor, Neuropathology, Pathology, Harvard Medical School, Massachusetts General Hospital, Boston, MA
1992 – 2006 Associate Professor with tenure, Pathology, Stanford University School of Medicine
2006 – Professor of Pathology (Neuropathology), Stanford University School of Medicine

Other Experience and Honors

1987 – 1995 Veterans' Administration Merit Review Board/Neurobiology (Ad hoc)
1990, 1995 NIH Neurological Disorders Program Project Special Review Committee
1987 – 1991 Associate Editor, *Journal of Immunology*
1993 – 1998 National Multiple Sclerosis Society Basic Sciences Study Section B
1994 – 1997 NIH AIDS & Related Research Study Section
1993 – 1995 Review Panel, *Human Pathology*
1996 – 1997 Editorial Board, *Neurology*
1991 – 2004 Editorial Board, Journal of Neuropathology and Experimental Neurology
2000 – Editorial Board, *Brain Pathology*
2000 – Editorial Board, *Journal of Neuroimmunology*
2001 – 2002 Vice President, American Association of Neuropathologists
2002 NIH Project Site Visit Panel and ad hoc reviewer for NIH NSD-C1 Study Section
2005 – 2007 Associate Editor, *Journal of Neuropathology and Experimental Neurology*
2007 – 2017 Editor-in-Chief, *Journal of Neuropathology and Experimental Neurology*
2011 – 2012 President, American Association of Neuropathologists

C. Contributions to Science (Publications selected from 235 peer-reviewed publications)

1. Identification of encephalitogenic determinants of myelin proteolipid protein (PLP) and development of widely used EAE models

   At the beginning of my research career, the only known antigen that induced EAE and was thought to be relevant to MS was myelin basic protein (MBP). I participated in the identification of numerous myelin proteolipid protein (PLP) and other myelin protein encephalitogenic epitopes, and the development of widely used mouse EAE models.

   a. Tuohy VK, Lu Z, Sobel RA, Laursen RA, Lees MB. Identification of an encephalitogenic determinant of myelin proteolipid protein for SJL mice. *J Immunol*, 1989 142: 1523-1527. PMID: 2465343.
   b. Bettelli E, Pagany M, Weiner HL, Linington C, Sobel RA, Kuchroo VK. Myelin oligodendrocyte glycoprotein-specific TCR transgenic mice develop spontaneous optic neuritis. *J Exp Med* 2003, 197:1073- 1081. PMCID: PMC2193967.
   c. Bettelli E, Baeten D, Jäger A, Sobel RA, Kuchroo VK. Myelin oligodendrocyte glycoprotein-specific T and B cells cooperate to induce a Devic-like disease in mice. *J Clin Invest*, 2006;116:2393-2402. PMCID: PMC1555670.

d. Shetty A, Gupta SG, Varrin-Doyer M, Weber MS, Prod'homme T, Molnarfi N, Ji N, Nelson PA, Patarroyo JC, Schulze-Topphoff U, Fogal S, Forsthuber T, Sobel RA, Bernard CCA, Slavin AJ, Zamvil SS. Immunodominant T cell epitopes of MOG reside in its transmembrane and cytoplasmic domains in EAE. *Neurology: Neuroimmunol Neuroinflam* August 14, 2014 vol. 1 no. 2 e22 PMCID: PMC4202928.

2. Characterization of in situ immune response mechanisms in EAE

I have had a longstanding interest in immunopathologic mechanisms of injury in CNS demyelinating diseases and continue to pursue projects in studies of both mouse models and MS-affected CNS tissues.

a. **Sobel RA**, Blanchette BW, Bhan AK, Colvin RB. The immunopathology of acute experimental allergic encephalomyelitis. II. Endothelial cell Ia expression increases prior to inflammatory cell infiltration. J Immunol, 1984;132:2402-2406. PMID: 6425402.
b. Xiao S, Brooks CR, **Sobel RA**, Kuchroo VK. Tim-1 is essential for induction and maintenance of IL-10 in regulatory B cells and their regulation of tissue inflammation. *J Immunol* 2015 Feb 15;194(4):1602-8. PMCID: PMC4346345.
c. Peters A, Burkett PR, **Sobel RA**, Buckley CD, Watson SP, Bettelli E, Kuchroo VK. Podoplanin negatively regulates CD4 effector T cell responses. *J Clin Invest* 2015, 125(1):129-140. doi:10.1172/JCI74685. PMCID: PMC3422678.

3. Characterization of molecular pathology in patients with MS

We have characterized alterations occurring in MS-affected CNS tissues to understand the pathogenesis of and consequences of demyelination in lesions and normal-appearing white matter.

a. **Sobel RA**, Mitchell ME, Fondren G. Intercellular adhesion molecule-1 (ICAM-1) in cellular immune reactions in the human central nervous system. *Am J Pathol* 1990, 136:1309-1316 PMCID: PMC1877574.
b. Maeda A, **Sobel RA**. Matrix metalloproteinases in the normal human central nervous system, microglial nodules and multiple sclerosis lesions. *J Neuropathol Exp Neurol,* 1996;55:300-309. PMID: 8786388.
c. **Sobel RA**. Ephrin A receptors and ligands in lesions and normal-appearing white matter in multiple sclerosis. *Brain Pathol*, 2005;15:35-45. PMID: 15779235.
d. **Sobel RA**. Editorial: A novel unifying hypothesis of multiple sclerosis. *J Neuropathol Exp Neurol,* 2008 67:1032-34. PMID:18978540.

Complete List of Published Work
http://www.ncbi.nlm.nih.gov/pubmed/?term=sobel+ra

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

Ongoing Research Support

R01 NS030843 (Kuchroo) 4/1/10 – 3/31/19
NIH / NINDS
Analysis of T cell responses to myelin proteolipid protein
This project examines immune responses to myelin proteolipid protein in experimental autoimmune encephalomyelitis.
Role: Co-Investigator

National Multiple Sclerosis Society (NMSS) (Zamvil) 10/1/14 – 9/30/17
Characterization of novel MOG T cell epitopes shared in EAE and MS
The goals of this project are to characterize how antigen-specific T cells contribute to pathogenesis and regulation of CNS autoimmunity.
Role: Co-Investigator

Completed Research Support

R01 NS063008 (Zamvil) 4/1/10 – 3/31/14
NIH / NINDS
Regulatory Monocytes in CNS Autoimmunity
This project investigates the roles of type II monocytes in EAE.
Role: Co-Investigator

W81XWH-11-1-0512 (Zabel) 2011 – 2014
DOD Idea Award
Targeting Chemerin Receptor CMKLR1 in Multiple Sclerosis
This projects studies inhibition of CNS inflammation by targeting the chemokine receptor CMKLR1.
Role: Co-Investigator

NMSS (UCSF Subcontract) (Zamvil) 4/1/12 – 3/31/15
Aquaporin-4 (AQP4)-specific T cells in CNS autoimmunity
This project investigates encephalitogenic epitopes of aquaporin-4.
Role: Co-Investigator

NMSS/Progressive MS Alliance (Stanford) (Sobel) 8/1/14 – 7/31/15
Azetidine-induced oligodendrogliopathy
This pilot project investigates effects of Azetidine on the mouse CNS.