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: Lawrence Steinman

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

POSITION TITLE: Professor of Neurology and Neurological Sciences and Pediatrics

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	BA	1968	Honors Physics
Harvard Medical School, Boston MA	MD	1973	Medicine
Weizmann Inst. Of Science, Rehovot Israel	Post-doc	1977	Chemical Immunology
Stanford University, Stanford, CA	Residency	1977-80	Neurology

A. Personal Statement
I have expertise in both cellular and molecular immunology, transcriptomics, proteomics and lipidomics. I chaired the Interdepartmental Program in Immunology at Stanford, and I am a Board Certified Neurologist. I have developed several therapies for multiple sclerosis (MS), with one achieving FDA approval-Natalizumab. I have a deep interest in the pathophysiology of MS, and the role of the adaptive immune system in the recognition of myelin and neuronal antigens. I have published extensively on molecular mimicry. I am quite familiar with all aspects of pre-clinical and clinical development of MS therapeutics. I recently was the Global Chief Investigator on two successful Phase 3 trials in relapsing remitting MS of Ublituximab for TG Therapeutics. We have published on tolerizing in gene therapy in MS, and in the use of altered peptide ligands in MS. Recently I helped to elucidate the molecular mimicry between EBNA-1 and GlialCAM, and its role in the pathogenesis of MS. Targeting the adaptive immune response to EBNA-1 and GlialCAM with approaches aimed at tolerization of the autoimmune response and eradication of the EBV infection in the B cell lineage in MS is the focus of my research efforts.

Ongoing and recently completed projects that I would like to highlight include:
Atara Therapeutics (PI: Steinman)   04/01/2019 – 06/01/2024

 "EBV in Multiple Sclerosis"
Role: Principal Investigator

2U01AI101984-06 (Paul Bolykky, PI, Steinman Co-Investigator)
06/1/2017- 06/30/2022   National Institutes of Health
 "Tregulatory Cells in EAE"

Novartis (PI Steinman)   04/01/2020 - 05/01/2022

High-dimensional analysis of immune subsets with mass cytometry and multiparameter flow cytometry in patients with Secondary Progressive Multiple Sclerosis Treated with Siponimod

Novartis (PI Steinman)   04/01/2020-05/01/2022
Pre-clinical Studies on Mechanism of Action of Siponimod with Mass Cytometry and Flow Cytometry

1R01NS11422001A1 Co-PI   (Michelle James, PI)   07/25/2020-
07/24/2025
National Institutes of Health
Imaging B cells in the brain and beyond: developing an immuno-PET toolbox to improve understanding and treatment of multiple sclerosis

Roche (PI Steinman)   10/01/21-9/30/25
High Dimensional Analysis of Cerebrospinal Fluid and Peripheral Blood from Multiple Sclerosis
CODEX, Proteomic, Lipidomic Analysis of MS Brain Lesions and CSF

B. Positions, Scientific Appointments, and Honors
Academic Posts
    2008-Present   Zimmermann Endowed Chair Stanford University
    2002 – 2011   Chairman, Stanford University, Interdepartmental Program in Immunology
    1991 – Present   Professor, Stanford, Depts. Neurology & Neurological Sciences & Pediatrics
    1980 – 1991   Assistant→ Associate Professor, Stanford, Neurology, Pediatrics and Genetics
Professional Awards & Prizes
    2017   **Elected Fellow American Association for Advancement of Science**
    2015   Fellow American Academy of Neurology
    2015   Cerami Prize for Translational Research
    2015   **Election to National Academy of Sciences-first neuroimmunologist elected**
    2011   Charcot Prize for Lifetime Achievement in MS
    2009   **Elected to Institute of Medicine, (renamed National Academy of Medicine**
    2008   Honorary PhD Universiteit Hasselt, Belgium
    2004   Stanford University Outstanding Inventor Award
    2004   John Dystel Prize for MS, National MS Society & Amer. Acad. of Neurology
    1994   Friedrich Sasse Award in Immunology from the Free University of Berlin
    1987 - 2002   Senator Jacob Javits Neuroscience Investigator Award, NIH, Twice Awarded
    1979   S. Weir Mitchell Award, American Academy of Neurology

    National Advisory Posts
    2015-2021   National Academy of Sciences Advisory Committee of Neurologic Complications
        of service in combat theaters of operation, starting 9/18 Chair Research Advisory
        Committee Gulf War Illness for the US Veterans Administration
    2006 – 2011   National Multiple Sclerosis Society Research Grant Review Committee
    1987 - 1990   National Institute of Medicine Advisory Committee on Pertussis Immunization
    1990 - 2015   Medical Advisory Board, Muscular Dystrophy Association
    1985, 1991-1996 Member, Immunologic Sciences Study Section, NIH
Board Certification
American Board of Psychiatry and Neurology (Neurology)
C. Contributions to Science
I have studied the pathogenesis of relapse and remission in multiple sclerosis. The work encompassed animal models, combined with analysis of the molecular pathology within MS brain material itself, and culminated in a major new therapy for MS. 1. We first isolated cloned T cells inducing relapsing paralysis and analyzed their precise specificities, T cell receptors, and homing receptors. 2.We then showed that alpha4 integrin was critical for lymphocyte traffic into MS brain. 3. We showed that a key receptor for this integrin, osteopontin, triggered neurological relapses, and then dissected the underlying molecular mechanisms. Osteopontin modulates pro- inflammatory

cytokine production and also serves as a survival molecule by inhibiting apoptosis of myelin reactive T cells, via its effect on the transcription factor, Fox03a.   4. Our analyses of MS lesions identified a key mediator of neurological remission, the protective chaperone, aB crystallin. We demonstrated how crystallin inhibits key aspects of brain inflammation and degeneration. We also identified other key molecules in lesions that are targeted by already approved drugs for other indications. We recently demonstrated that within the central nervous system in MS, there are clonal expansions of antibodies that target a portion of EBNA-1. The epitope is a molecular mimic of GlialCAM. 5. Although our work has produced a highly effective approved treatment for more than 275,000 patients with multiple sclerosis, we are driving towards antigen specific approaches to treat MS, and we have taken them so far into Phase 2B in the clinic.

Contribution 1:
a)Zamvil S, Nelson P, Trotter J, Mitchell D, Knobler R, Fritz R and Steinman L. T cell clones specific for myelin basic protein induce chronic relapsing EAE and demyelination. Nature, 317:355-358, 1985 PMID: 24133634
b)Oksenberg JR, Panzara MA, Begovich AB, Mitchell D, Erlich HA, Murray RS, Shimonkevitz R, Sherritt M, Rothbard J, Bernard CCA, and Steinman L. Selection for T cell receptor Vb-Db-Jb gene rearrangements with specificity for a myelin basic protein peptide in brain lesions of multiple sclerosis. Nature, 362:68-70, 1993. PMID: 7680433
c)Steinman L. Immunology of Relapse and Remission in Multiple Sclerosis. Annu Rev Immunol. 32:257-81, 2014. doi: 10.1146/annurev-immunol-032713-120227. PMID: 24438352

Contribution 2:
a)Yednock T, Cannon C, Fritz L, Sanchez-Madrid F, Steinman L, and Karin N. Prevention of experimental autoimmune encephalomyelitis by antibodies against a4b1 integrin. Nature, 356:63-66, 1992. PMID: 1538783
b)Steinman L. The Discovery of Natalizumab, A Potent Therapeutic for Multiple Sclerosis. Journal of Cell Biology 199(3):413-6, 2012 PMID: 23109666 PMCID: PMC3483125

Contribution 3:
a)Chabas D, Baranzini S, Mitchell D, Bernard CCA, Rittling S, Denhardt, D, Sobel R, Lock C, Karpuj M, Pedotti R, Heller R, Oksenberg J, Steinman L. The influence of the proinflammatory cytokine, osteopontin, on autoimmune demyelinating disease. *Science,* 294:1731-1735, 2001. PMID: 11721059
b)Steinman L. A molecular trio in relapse and remission for multiple sclerosis. Nature Reviews Immunology, 9:440-447, 2009 PMID: 19444308

Contribution 4:
a)Ousman S, Tomooka B, Van Noort J, Wawrousek E, O'Conner K, Hafler D, Sobel R, Robinson W, Steinman L. Protective and therapeutic role for aB-crystallin in autoimmune demyelination. *Nature*, 448:474-479, 2007. PMID: 17568699
b)Han MH, Hwang S, Roy DB, Lundgren DH, Price JV, Ousman S, Fernald G, Gerlitz B, Robinson WH, Baranzini SE, Grinnell BW, Raine CS, Sobel RA, Han DK, and Steinman L. Proteomic Analysis of Active Multiple Sclerosis Lesions Reveals Therapeutic Targets. *Nature*, 451:1076-1081, 2008. PMID: 18278032
c)Kurnellas MP, Adams CM, Sobel RA, Steinman L and Rothbard JR. Amyloid Fibrils Composed of Hexameric Peptides Attenuate Neuroinflammation. *Science Translational Medicine*, 179 179ra42, 2013 PMID: 23552370 PMCID: PMC3684024
d)Rothbard JB, Rothbard JJ, Soares L, Fathman CG, Steinman L. Identification of a common immune regulatory pathway induced by small heat shock proteins, amyloid fibrils, and nicotine. Proc Natl Acad Sci U S A. 2018 Jul 3;115(27):7081-7086. doi: 10.1073/pnas.1804599115. Epub 2018 Jun 18.PMID: 29915045, PMCID, PMC6142248

Contribution 5:
a)Robinson, WH, Fontoura P, Lee BJ, Neuman de Vegvar HE, Tom J, Pedotti R, DiGennaro C, Mitchell DJ, Fong D, Ho PK, Ruiz P, Maverakis E, Stevens D, Bernard CCA, Olsson T, Martin R, Kuchroo VK, van Noort JM, Genain CP, Utz PJ, Garren H, and Steinman L. Protein microarrays guide tolerizing DNA vaccine treatment of autoimmune encephalomyelitis, *Nature Biotechnology* 21:1033-1039, 2003. PMID: 12910246

b)Garren H, Robinson W, Krasulová E, Havrdová E, Nadj C, Selmaj K, Losy J, Nadj I, Radue EW, Kidd BA, Gianettoni J, Tersini K, Utz PJ, Valone F, Steinman L and the BHT-3009 Study Group. Phase 2b Trial of a DNA Vaccine Encoding Myelin Basic Protein in Relapsing Multiple Sclerosis. *Annals of Neurology*, 63(5):611- 620, 2008 PMID: 18481290

c) Moreno MA, Or-Geva N, Aftab BT, Khanna R, Croze E, Steinman L, Han MH. Molecular signature of Epstein-Barr virus infection in MS brain lesions. Neurol Neuroimmunol Neuroinflamm. 2018 Jul;5(4):e466. doi: 10.1212/NXI.0000000000000466. eCollection 2018 Jul. PubMed PMID: 29892607; PubMed Central PMCID: PMC5994704.

d)Lanz TV, Brewer RC, Ho PP, Moon JS, Jude KM, Fernandez D, Fernandes RA, Gomez AM, Nadj GS, Bartley CM, Schubert RD, Hawes IA, Vazquez SE, Iyer M, Zuchero JB, Teegen B, Dunn JE, Lock CB, Kipp LB, Cotham VC, Ueberheide BM, Aftab BT, Anderson MS, DeRisi JL, Wilson MR, Bashford-Rogers RJM, Platten M, Garcia KC, Steinman L, Robinson WH. Clonally Expanded B Cells in Multiple Sclerosis Bind EBV EBNA1 and GlialCAM. Nature. 2022;doi:10.1038/s41586-022-04432-7. [Epub ahead of print] PubMed PMID: 35073561.
e)Robinson WH, Steinman L. Epstein-Barr virus and multiple sclerosis. Science. 2022 Jan 21;375(6578):264-265. doi: 10.1126/science.abm7930. Epub 2022 Jan 13. PubMed PMID: 35025606.

My Bibliography
https://www.ncbi.nlm.nih.gov/myncbi/1TsRqc-GY5mQG/bibliography/public/