## BIOGRAPHICAL SKETCH

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NAME: Lawrence Steinman

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

POSITION TITLE: Professor

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 MS, with one achieving FDA approval-Natalizumab.

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.

### B. Positions and Honors

Academic Posts

1980 – 1985 Assistant Professor, Stanford University, Depts. Neurology & Pediatrics
1985 – 1991 Associate Professor, Stanford University, Depts. Neurology, Pediatrics and Genetics
1991 – Present and Professor, Stanford University, Depts. Neurology & Neurological Sciences, Genetics Pediatrics
2002 – 2011 Chairman, Stanford University, Interdepartmental Program in Immunology
2008 George A. Zimmermann Endowed Chair Stanford University, inaugurated

Professional Awards & Prizes

1979 S. Weir Mitchell Award, American Academy of Neurology
1987 - 2002 Senator Jacob Javits Neuroscience Investigator Award, NIH, Twice Awarded
1994 Friedrich Sasse Award in Immunology from the Free University of Berlin
2004 John Dystel Prize for MS, National MS Society & Amer. Acad. of Neurology
2004 Stanford University Outstanding Inventor Award
2008 Honorary PhD Universiteit Hasselt, Belgium
2009 **Elected to Institute of Medicine, renamed (2015) National Academy of Medicine**
2011 Charcot Prize for Lifetime Achievement in MS Research
2015 **Election to National Academy of Sciences-first neuroimmunologist ever elected**
2015 Cerami Prize for Translational Research

2015 Fellow American Academy of Neurology
2017 **Elected Fellow American Association for Advancement of Science**

Advisory Posts

1985 & 1991 - 1996 Member, Immunologic Sciences Study Section, NIH
1990 - Present Medical Advisory Board, Muscular Dystrophy Association
1987 - 1990 National Institute of Medicine Advisory Committee on Pertussis Immunization
1988 - 1991 National Multiple Sclerosis Society Medical Advisory Committee
2006 – 2011 National Multiple Sclerosis Society Research Grant Review Committee
National Academy of Sciences Advisory Committee of Neurologic Complications of Military Service in Theaters of Combat Operations

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. 5. Although our work has produced a highly effective approved treatment for more than 225,000 patients with multiple sclerosis, we are driving towards antigen specific approaches to treat autoimmune disease, and have taken them so far into Phase 2B in the clinic. The work on tolerance involves extensive analysis of autoantibodies on microarrays and with proteomic techniques.

**Contribution 1:**

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

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

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:**

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

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:**

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

Steinman L. A molecular trio in relapse and remission for multiple sclerosis. Nature Reviews Immunology, 9:440-447, 2009 PMID: 19444308

**Contribution 4:**

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

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

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

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:**

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

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

Roep BO, Solvason N, Gottlieb PA, Abreu JRF, Harrison LC, Eisenbarth GS, Yu L, LevitenM, Hagopian WA, Buse JB, von Herrath M, Quan J, King R, Robinson WH, Utz PJ, Garren H, the BHT 3021 Investigtors and Lawrence Steinman. Plasmid encoded proinsulin preserves C-peptide while specifically reducing proinsulin specific CD8 T cells in type 1 diabetes. *Science Translational Medicine*, Jun 26;5(191):191ra82. doi: 10.1126/scitranslmed.3006103, 2013 PMID: 23803704 PMCID: PMC4516024

Steinman L. The Road Not Taken: Antigen-Specific Therapy and Neuroinflammatory Disease. *JAMA Neurology*, 1:1-2. doi: 10.1001/jamaneurol.2013.3553. PMID: 23817885

Ho PP, Lahey LJ, Mourkioti F, Kraft PE, Filareto A, Brandt M, Magnusson KEG, Finn EE, Chamberlain JS, Robinson WH, Blau HM, **Steinman L**. Engineered DNA plasmid reduces immunity to dystrophin while improving muscle force in a model of gene therapy of Duchenne dystrophy. Proc Natl Acad Sci U S A. 2018 Sep 4. pii: 201808648. doi: 10.1073/pnas.1808648115.

My Bibliography
https://www.ncbi.nlm.nih.gov/sites/myncbi/1xljole3G2c5mw/bibliography/57713587/public/?sort=date&direction=ascending

D. **Additional Information: Research Support**

**Ongoing Research Support**

**ACTIVE**

**Atara Therapeutics** (PI: Steinman) 04/01/2019 – 06/01/2022
"EBV in Multiple Sclerosis"
Role: Principal Investigator
No Overlap with this application.

**2U01AI101984-06** (Paul Bolykky, PI) 06/1/2017- 06/30/2022
National Institutes of Health
Cooperative Study Group for Autoimmune Disease Prevention (U01)
"Tregulatory Cells in EAE"
Role: Co-Investigator
No Overlap with this application.

**Novartis** (PI Steinman) 04/01/2020 - 05/01/2021
High-dimensional analysis of immune subsets with mass cytometry and multiparameter flow cytometry in patients with Secondary Progressive Multiple Sclerosis Treated with Siponimod
No Overlap with this application.

**Novartis** (PI Steinman) 04/01/2020-05/01/2021
Pre-clinical Studies on Mechanism of Action of Siponimod with Mass Cytometry and Multidimensional Flow Cytometry
No Overlap with this application.

**1R01NS11422001A1 Co-PI**
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

**Completed Research Support**

LeDucq Fondation 01/2014 - 12/2019
"Sphingosine 1-phosphate in neurovascular biology and disease (SphingoNet)"
Mechanism of S1P inhibition in EAE

ML29966 (Steinman, PI) 03/01/2017 - 11/01/2020
Genentech
"CyToF Studies with Ocrelizumab"
An open-label, multicenter, biomarker study to explore the mechanism of action of ocrelizumab and B-cell biology in patients with relapsing multiple sclerosis or primary progressive multiple sclerosis
The major goals of this project are to study with CyToF immune cells in patients treated with Ocrelizumab