

## BIOGRAPHICAL SKETCH

NAME: Jeffrey L. Bennett, M.D., Ph.D.

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

POSITION TITLE: Professor of Neurology and Ophthalmology

**EDUCATION/TRAINING:**

INSTITUTION AND LOCATION	DEGREE	Completion Date MM/YYYY	FIELD OF STUDY
Case Western Reserve University, Cleveland, OH	BA	1986	Biochemistry, Philosophy
Stanford University School of Medicine, Stanford, CA	MD	1993	
Stanford University School of Medicine, Stanford, CA	PhD	1993	Biophysics
University of Colorado School of Medicine, Denver, CO	Internship	1994	Internal Medicine
University of Colorado School of Medicine, Department of Neurology, Denver, CO	Resident	1997	Neurology
University of Colorado, Department of Molecular, Cellular and Developmental Biology, Boulder, CO	Post-doc	1997	Developmental Biology
University of Pennsylvania, Department of Neurology, Philadelphia, PA	Fellow	1998	Neuro-Ophthalmology

### A. Personal Statement

As a clinician-scientist, my research is directed at understanding the pathophysiology of autoimmune CNS demyelination and using this knowledge to prevent neurologic and visual disability in affected individuals. My laboratory has made significant strides in understanding the humoral and cellular immune pathology driving two major CNS inflammatory disorders: multiple sclerosis (MS) and neuromyelitis optica (NMO). Our main interests have included identifying disease-specific antigens, understanding MS and NMO pathogenesis, identifying novel biomarkers of disease activity, and developing new therapeutic strategies. Our laboratory has taken a leading position in MS and NMO research through the derivation of recombinant monoclonal antibodies (rAbs) from clonally expanded cerebrospinal fluid plasma cells. Using our compendium of patient-derived AQP4-specific rAbs in NMO and myelin-specific rAbs in MS, we have established autoantibody pathogenicity, developed novel *ex vivo* and *in vivo* disease models, dissected the molecular mechanisms driving disease pathogenesis, and developed novel antigen specific blocking therapies for the treatment of affected patients.

### B. Positions and Honors

#### Positions and Employment

1998 - 2005	Assistant Professor of Neurology and Ophthalmology, University of Colorado School of Medicine (CUSOM), Aurora, CO
2005 - 2009	Associate Professor of Neurology and Ophthalmology, CUSOM
2009 -	Professor, Neurology and Ophthalmology, CUSOM
2011 -	Associate Director, Translational Research, Center for Neuroscience (CNS), CUSOM
2011 -	Graduate Faculty, Program in Neuroscience, Program in Toxicology, CUSOM

#### Other Experience and Professional Memberships

Member, American Academy of Neurology (AAN); elected Fellow, 2010  
 Member, American Neurological Association (ANA); elected Fellow, 2006  
 Member, Association for Research in Vision and Ophthalmology (ARVO)  
 Member, North American Neuro-Ophthalmologic Society (NANOS); elected Fellow, 2008  
 Editorial Boards: Journal of Neuro-ophthalmology (Editorial Board 2010-17), Ophthalmology, Multiple Sclerosis (Editorial Board 2012-2017), Neurology: Neuroimmunology & Neuroinflammation (Editorial Board 2015-)

1994 - Physician License, Colorado; Pennsylvania (1997-1998)  
 1998, 2008 Board Certification in Neurology, American Board of Psychiatry and Neurology  
 2004 Ad-hoc Reviewer, Institute of Neurology, Medical Research Council, United Kingdom  
 2006 - 2008 Ad-hoc Reviewer, National Multiple Sclerosis Society  
 2006 - 2016 Standing Member, Review Committees A, B and D, National Multiple Sclerosis Society  
 2007 Ad-hoc Reviewer, Fight for Sight and Neurological Foundation of New Zealand  
 2007 Abstract Committee, American Neurologic Association Meeting  
 2008 Scientific Review Committee, World Congress on Treatment & Research in Multiple Sclerosis  
 2008 - 2010 Chair, Multiple Sclerosis Peer Review Panel, American Institute of Biological Sciences  
 2008 - 2012 Abstract Committees: Neuro-ophthalmology of Multiple Sclerosis, and AAN  
 2009 Ad-hoc Reviewer, ZNS1 SRB-M, National Institute of Neurological Disorders & Stroke (NINDS)  
 2009 - 2010 Ad-hoc Reviewer, ZRG1 BDCN-T (58), RFA-OD-09-003 Challenge Grant Panel 11  
 2009 - 2013 Ad-hoc Reviewer, Anterior Eye Disease (AED) Study Section, NEI  
 2010 Chairman, MS2 Pathogenesis/Etiology Panel, American Institute of Biological Sciences  
 2011 Ad-hoc Reviewer, Austrian Science Fund (FWF)  
 2013 - present Ad-hoc Reviewer & Member, Diseases & Pathophysiology of the Visual System (DPVS)

## Honors

1982 National Merit Scholar, Western Reserve Scholar, and Andrew Squires Scholar, Case Western Reserve University (CWRU)  
 1985 Junior Award, Harriet Pullman Award, Phi Beta Kappa Award, and Hardy Philosophical Prize, Case Western Reserve University  
 1985 Student Research Award, Society of Nuclear Medicine  
 1986 Mortar Board Society & Phi Beta Kappa  
 1986 Medical Scientist Training Program Awardee, National Institute of General Medical Sciences  
 1986 Summa cum laude, Case Western Reserve University  
 1996 Scholarship for Residents, American Academy of Neurology  
 1997 Chief Resident, Department of Neurology, University of Colorado School of Medicine  
 1999 Individual Investigator Award, Howard Hughes Medical Institute  
 2000 Basil O'Connor Starter Scholar Award, March of Dimes  
 2004 - Best Doctors in America (elected by neurologic colleagues)  
 2006 Stephen C. Reingold Research Award, National Multiple Sclerosis Society  
 2011 - America's Top Physicians  
 2012 - Best Doctors, US News and World Report  
 2013 CU Inventor of the Year

## **C. Contribution to Science**

1. We have employed single cell sorting and RT-PCR technology to investigate the B cell repertoires in optic neuritis (ON), multiple sclerosis (MS), and neuromyelitis optica (NMO). Our investigations have demonstrated that intrathecal inflammation in idiopathic ON, MS, and NMO demonstrate features of an antigen-driven response, predominantly composed of short-lived plasmablasts. The repertoires demonstrate biased usage of heavy-chain variable region gene segments and disease-specific patterns of somatic hypermutation. The results have provided a novel metric for the diagnosis of MS and illustrated the potential role of CNS B cells in NMO relapse.
  - a. Owens GP, Winges KM, Ritchie AM, Edwards S, Burgoon MP, Lehnhoff L, Nielsen K, Corboy J, Gilden DH, **Bennett JL**. VH4 gene segments dominate the intrathecal humoral immune response in multiple sclerosis. *J Immunol* 179:6343-51, 2007. PMID: **17947712**.
  - b. **Bennett JL**, Haubold K, Ritchie AM, Edwards SJ, Burgoon M, Shearer AJ, Gilden DH, Owens GP. CSF IgG heavy-chain bias in patients at the time of a clinically isolated syndrome. *J Neuroimmunol*. 2008; 199:126-32. PMCID: **PMC2572301**.

- c. Cameron EM, Spencer S, Lazarini J, Harp CT, Ward ES, Burgoon M, Owens GP, Racke MK, **Bennett JL**, Frohman EM, Monson NL. Potential of a unique antibody gene signature to predict conversion to clinically definite multiple sclerosis. *J Neuroimmunol* 213:123-30, 2009. PMID: **PMC2785005**.
  - d. Kowarik MC, Dzieciatkowska M, Wemlinger S, Ritchie AM, Hemmer B, Owens GP, **Bennett JL**. The cerebrospinal fluid immunoglobulin transcriptome and proteome in neuromyelitis optica reveals central nervous system-specific B cell populations. *J Neuroinflammation* 12:19, 2015. PMID: **PMC4323273**.
2. We have generated recombinant monoclonal antibodies from MS and NMO patients and used them to identify and validate targets of the immune response. We published a seminal paper demonstrating that aquaporin-4 (AQP4) autoantibodies are produced by plasmablasts in the CSF of NMO patients and cause disease pathology in animal models. In MS, we have shown that the antibodies produced by CSF plasmablasts are not directed against Epstein-Barr virus, but have identified novel putative MS antigens with pathogenic potential. We have recently identified a novel blood-brain barrier target in NMOSD patients and collaborated to investigate B cell checkpoints in NMOSD.
    - a. **Bennett JL**, Lam C, Kalluri SR, Saikali P, Bautista K, Dupree C, Glogowska M, Case D, Antel JP, Owens GP, Gilden D, Nessler S, et al. Intrathecal pathogenic anti-aquaporin-4 antibodies in early neuromyelitis optica. *Ann Neurol*. 2009; 66:617-29. PMID: PMC3180961.
    - b. Blauth K, Soltys J, Matschulat A, Reiter CR, Ritchie A, Baird NL, Bennett JL, Owens GP. Antibodies produced by clonally expanded plasma cells in multiple sclerosis cerebrospinal fluid cause demyelination of spinal cord explants. *Acta Neuropathol* 130:765-781, 2015. PMID: **PMC4655138**.
    - c. Shimizu F, Schaller KL, Owens GP, Cotleur AC, Kellner D, Takeshita Y, Obermeier B, Kryzer TJ, Sano Y, Kanda T, Lennon VA, Ransohoff RM, **Bennett JL**. Glucose-regulated protein 78 autoantibody associates with blood-brain barrier disruption in neuromyelitis optica. *Science Translational Medicine*, 9(397), 2017. PMID: **PMC5585784**.
    - d. Cotzomi E, Stathopoulos P, Lee CS, Ritchie AM, Soltys JN, Delmotte FR, Oe T, Sng J, Jiang R, Ma AK, Vander Heiden JA, Kleinstein SH, Levy M, **Bennett JL**, Meffre E, O'Connor KC. Early B cell tolerance defects in neuromyelitis optica favour anti-AQP4 autoantibody production. *Brain*. 2019. doi: 10.1093/brain/awz106.
  3. My laboratory has used AQP4-specific rAbs derived from NMO patients to characterize the binding of AQP4 autoantibody to target antigen, dissect the role of antibody effector mechanisms in NMO lesion pathogenesis, understand the mechanisms of myelin injury in NMO and MS, and evaluate myelin recovery after NMO and MS injury. My laboratory research studies continue to focus on understanding glial injury in NMO and MS.
    - a. Herwerth M, Kalluri SR, Srivastava R, Kleele T, Kenet S, Illes Z, Merkler D, **Bennett JL**, Misgeld T, Hemmer B. In vivo imaging reveals rapid astrocyte depletion and axon damage in a model of neuromyelitis optica-related pathology. *Ann Neurol* 79:794-805, 2016. PMID: **PMC5021140**.
    - b. Weil MT, Möbius W, Winkler A, Ruhwedel T, Wrzos C, Romanelli E, **Bennett JL**, Enz L, Goebels N, Nave KA, Kerschensteiner M, Schaeren-Wiemers N, Stadelmann C, Simons M. Loss of Myelin Basic Protein Function Triggers Myelin Breakdown in Models of Demyelinating Diseases. *Cell Rep*. 2016 Jul 12;16(2):314-22. PMID: **PMC4949381**.
    - c. Liu Y, Given KS, Owens GP, Macklin WB, **Bennett JL**. Distinct patterns of glia repair and remyelination in antibody-mediated demyelination models of multiple sclerosis and neuromyelitis optica. *Glia* 2018;66:2575-2588. PMID: **PMC6309481**.
    - d. Soltys J, Liu Y, Ritchie A, Wemlinger S, Schaller K, Schumann H, Owens GO, **Bennett JL**. Membrane Assembly of Aquaporin-4 Autoantibodies Regulates Classical Complement Activation in Neuromyelitis Optica. *J Clin Invest*. 2019; 129:2000-2013. PMID: **30958797**
  4. Using our recombinant antibody technology, we have developed multiple therapeutic approaches for treating AQP4 seropositive NMO patients. Methods have included antibody blocker therapies, peptoid ligands, small molecule inhibitors, and anti-idiotypic therapies. The antibody blocker therapy "aquaporin-4" has led to a patent application, and the therapeutic molecule is under development for clinical trials in NMO.
    - a. Tradtrantip L, Zhang H, Saadoun S, Phuan PW, Lam C, Papadopoulos MC, **Bennett JL**, Verkman AS. Anti-aquaporin-4 monoclonal antibody blocker therapy for neuromyelitis optica. *Annals of neurology*. 2012; 71(3):314-22. PMID: **PMC3314396**.

- b. Tradtrantip L, Zhang H, Anderson MO, Saadoun S, Phuan PW, Papadopoulos MC, **Bennett JL**, Verkman AS. Small-molecule inhibitors of NMO-IgG binding to aquaporin-4 reduce astrocyte cytotoxicity in neuromyelitis optica. FASEB J. 2012 May;26(5):2197-208. Epub 2012 Feb 8. PMCID: **PMC3336779**.
- c. Raveendra BL, Wu H, Baccala R, Reddy MM, Schilke J, **Bennett JL**, Theofilopoulos AN, Kodadek T. Discovery of peptoid ligands for anti-aquaporin 4 antibodies. Chemistry & biology. 2013; 20(3):351-9. PMCID: **PMC3640264**.
- d. **Bennett JL**, Owens GP, Verkman AS, inventors. The Regents of the University of Colorado, applicant. Compositions and methods for the treatment of neuromyelitis optica. WO2012145746 A1. 2012 April 23. [patent application]

Complete List of Published Work in My Bibliography:

<http://www.ncbi.nlm.nih.gov/sites/myncbi/jeffrey.bennett.1/bibliography/44568683/public/?sort=date&direction=descending>