BIOGRAPHICAL SKETCH

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NAME: Dorothy Anne Haney Cross

eRA COMMONS USER NAME: ANNE_CROSS

POSITION TITLE: Professor of Neurology and The Manny and Rosalyn Rosenthal - Dr. John L. Trotter MS Center Chair in Neuroimmunology

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
U. of South Alabama, Mobile, AL	B.S.	1973-76	Chemistry
U. of Alabama, Birmingham, AL	M.D.	1976-80	Medicine
Mercy Hospital & Medical Center, San Diego CA		1980-81	Medical Internship
George Washington U., Washington, D.C.		1981-84	Neurology Residency
National Institutes of Health, NINDS		1984-86	Neuroimmunology fellowship

NOTE: The Biographical Sketch may not exceed five pages. Follow instructions below.

A. Personal Statement

Dr. Cross is Section Head of Neuroimmunology, with over 30 years of experience as a clinical neurologist specialized in the area of multiple sclerosis, and in MS research. She has trained 17 graduate students and post-doctoral fellows since coming to Washington University in 1991. She has extensive experience in doing work in animal models of MS (since 1984), and in human imaging research (since 2002). She was the principal investigator of a single site study of rituximab in MS patients failing primary disease-modifying therapies, that was funded by the National MS Society and the NIH, which was one of the first studies to examine the effects of B cell depletion in MS.

B. Positions and Honors

1984-1986 Medical Staff Fellow, Neuroimmunology Branch, National Institutes of Health, Bethesda, Maryland
1986-1987 Levy Fellow, Dept. of Virology and Molecular Biology, St. Jude Children's Research Hospital, Memphis, Tennessee
1987-1990 Fellow of the National MS Society, Dept. of Pathology, Albert Einstein College of Medicine
1990-1991 Assistant Professor of Neurology and Pathology, Albert Einstein College of Medicine
1991-1998 Assistant Professor of Neurology, Washington University School of Medicine
1998-2002 Associate Professor of Neurology, Washington University School of Medicine
1992 - 2001 co-Director Washington University Multiple Sclerosis Center
2001 - Section Head, Neuroimmunology; Director Washington University Multiple Sclerosis Center
2003- Professor of Neurology, Washington University School of Medicine

Other Experience and Professional Memberships

1996 – to 1998 Editorial Board member, Journal of Neuropathology and Experimental Neurology
1996 – to 2004 Editorial Board member, Neurology
1996 – to present Editorial Board member, Journal of Neuroimmunology
1982 – to present Member American Academy of Neurology

1987 – to present Member of the International Society of Neuroimmunology
2008- 2111 Executive Committee Member, National Clinical Advisory Board of the National MS Society
2006-2008 Planning committee member, First Keystone Symposium on Multiple Sclerosis, held Santa Fe, NM
2007-2013 Member, Research Programs Advisory Committee, National MS Society USA
2007 Editor, CONTINUUM on Multiple Sclerosis (AAN publication)
2011- 2015 Member, Board of Scientific Counselors, NINDS/NIH
2012-2015 Board of Directors, America's Committee for Treatment and Research in MS -ACTRIMS
2013- 2016 Chair, Research Programs Advisory Committee, National MS Society USA

Honors

1972 United States Presidential Scholar
1973 National Merit Scholarship Recipient
1976 Phi Kappa Phi
1978 Alpha Omega Alpha
1977, 78, 80 Superior Scholastic Achievement Certificate, University of Alabama School of Medicine
1980 Award for Academic Excellence, American Medical Women's Association
1987-1990 Fellow of the National Multiple Sclerosis Society
1990-1995 Harry Weaver Neuroscience Scholar of the National Multiple Sclerosis Society
1996 – Elected to Membership in American Neurological Association
1996-1999, 2001 Selected as one of "Best Doctors in America", Central Region
2002-2004 Selected as one of "Best Doctors in America"
2003 - The Manny and Rosalyn Rosenthal - Dr. John Trotter MS Center Chair in Neuroimmunology
2007-2015 Selected as one of "Best Doctors in America"
2010 President's Achievement Award, Barnes-Jewish Hospital Foundation
2014 Faculty Achievement Award, Washington University School of Medicine

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C. Contribution to Science

1. As a post-doctoral fellow, I became interested in how immune cells gain access to the central nervous system (CNS), which was considered "immune privileged." I followed radiolabeled myelin-reactive T cells day-by-day into the CNS of mice passively induced to develop experimental autoimmune encephalomyelitis (EAE), identifying them initially in the meninges and perivascular spaces. I was among the first investigators to study the blood brain barrier (BBB) function using the EAE model in the 1980's and early 1990's, including being amongst the first to investigate roles of adhesion-related molecules in the migration of inflammatory/immune cells into the CNS. Eventually, the adhesion molecule VLA-4 was identified as critical in MS, leading to the development of the highly effective MS drug, natalizumab, to block it.

a) Cross AH, Cannella B, Brosnan CF, Raine CS: Homing to central nervous system vasculature by antigen specific lymphocytes. I. Localization of 14C-labeled cells during acute, chronic and relapsing experimental allergic encephalomyelitis. Lab Invest 1990;63:162-170
b) Cannella B, Cross AH, Raine CS: Up-regulation and co-expression of adhesion molecules correlate with relapsing autoimmune demyelination in the central nervous system. J Exp Med 1990;172:1521-1524
c) Cross AH, Cannella B, Brosnan CF, Raine CS: Hypothesis:Antigen-specific T cells prime CNS endothelium for recruitment of nonspecific inflammatory cells to effect autoimmune demyelination. J Neuroimmunol 1991;33:237-244
d) Cross AH, Raine CS: CNS endothelial cell-polymorphonuclear cell interactions during autoimmune demyelination. Am J Path 1991;139:1401-1409 PMCID: PMC1886454

2. After setting up my laboratory at Washington University in late 1991, I became interested in the potential role of nitrogen radicals and oxygen radicals in MS. I was among the first investigators to study the roles of nitric oxide and peroxynitrate in the EAE model, and in tissues and CSF of patients with MS. Utilizing the novel

method of electron paramagnetic resonance and together with colleagues in the Dept of Chemistry, I identified reactive nitrogen species (RNS) in the CNS during active EAE. We identified cellular sources of RNS in EAE. My laboratory then demonstrated the pathologic potential of RNS, by using specific inhibitors of inducible nitric oxide synthase to reduce the clinical and pathologic severity of the EAE model.

a) Lin RF, Lin T-S, Tilton RG, Cross AH: Nitric oxide localized to spinal cords of mice with experimental allergic encephalomyelitis. An electron paramagnetic resonance study. J Exp Med 1993;178:643-648
b) Cross AH, Misko TP, Lin RF, Hickey WF, Trotter JL, Tilton RG: Aminoguanidine, an inhibitor of inducible nitric oxide synthase, ameliorates experimental autoimmune encephalomyelitis. J Clin Invest 1994;93:2684-2690 PMCID: PMC294515
c) Cross AH, Keeling RM, Goorha S, San M, Rodi C, Wyatt PS,Manning PT, Misko TP: Inducible nitric oxide synthase gene expression and enzyme activity correlate with disease activity in adoptively-transferred murine EAE. J. Neuroimmunol. 1996; 71:145-153
d) Cross AH, Manning PT, Keeling RM, and Misko TP: Peroxynitrite formation within the central nervous system in active multiple sclerosis. J. Neuroimmunol. 1998; 88:45-56.

3. Presence of immunoglobulins in the spinal fluid is found in >85% of MS patients, and is useful for diagnosis. The source is likely plasma cells and B lymphocytes found within the CNS – inside the BBB. My laboratory identified the critical role of B lymphocytes in the C57BL/6 EAE model induced using recombinant extracellular myelin oligodendrocyte glycoprotein (MOG). This led to studies in humans showing excessive intrathecal immunoglobulins correlated with worse MS. In 2000, I proposed a single site trial of B cell depletion in humans with MS in a grant application to the National MS Society. We were funded by the NMSS and in early 2002. In Spring 2002, we began an investigator-initiated trial of the anti-CD20 monoclonal antibody, rituximab (which was FDA-approved only for non-Hodgkin's lymphoma at that time) as an add-on therapy in patients who were failing treatment with beta-interferon or glatiramer acetate.

a) Lyons JA, San M, Happ MP, and Cross AH: B-cells are critical to induction of experimental allergic encephalomyelitis by protein but not by a short encephalitogenic peptide. Eur. J. Immunol.1999; 29: 3432-3439.
b) Cross AH, Stark JL, Ramsbottom MJ, Lauber J, Lyons JA: Rituximab reduces B cells and T cells in cerebrospinal fluid of multiple sclerosis patients. J. Neuroimmunol. 2006; 180:63-70. PMCID: PMC1769354
c) Naismith RT, Piccio L, Lyons JA, Lauber J, Tutlam NT, Parks BJ, Trinkaus K, Song SK, Cross AH: Rituximab add-on therapy for breakthrough relapsing multiple sclerosis: a 52-week phase II trial. Neurology 2010; 74: 1860-1867 PMCID: PMC2882224
d) Piccio L, Naismith RT, Trinkaus K, Klein RS, Parks BJ, Lyons JA, Cross AH. Changes in B and T lymphocytes and chemokines with rituximab treatment in multiple sclerosis. Arch Neurol 2010; 67: 707-714. PMCID: PMC2918395

4. The understanding of MS has been hampered by lack of access to CNS tissues during the course of the disease, which typically lasts for decades. To help counter this barrier, I have worked with several collaborators in Radiology to improve imaging methods for MS, to help understand the ongoing and changing pathology of the disease. One key collaborator is Dr. Sheng-Kwei Song. We investigated diffusion tensor imaging (a type of MRI) as a way to measure demyelination and axon loss using animal models of MS and then in MS patients. We have now developed much better diffusion methodologies, including diffusion basis spectrum imaging, to account for inflammation, and are now applying these methods to humans with MS and related diseases. The first citation below (a) has been cited over 1500 times in the published literature.

a) Song, SK, Sun S-W, Ramsbottom MJ, Chang C, Russell J, Cross AH: Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. Neuroimage 2002; 17: 1429-1436.
b) Naismith RT, Xu J, Tutlam N, Scully PT, Trinkaus K, Snyder AZ, Song SS, Cross AH. Increased Diffusivity in Acute Multiple Sclerosis Lesions Predicts Risk of Black Holes. Neurology 2010; 74:1694-701. PMCID2882210
c) Wang Y, Wang Q, Haldar JP, Yeh FC, Xie M, Sun P, Trinkaus K, Klein RS, Cross AH, Song S-K. Quantification of increased cellularity during inflammatory demyelination. Brain 2011; 134: 3587-9 PMCID: PMC3235568
d) Wang Y, Sun P, Wang Q, Trinkaus K, Naismith RT, Cross AH, Song SK. Differentiation and quantification of inflammation, demyelination, and axon injury/loss in MS. Brain.2015;138(Pt 5):1223-38.PMCID: PMC4407189

5. Working with my former post-doctoral fellow and now key collaborator Dr. Laura Piccio, our laboratories have examined the roles of adipokines in animal models of MS, and are currently investigating whether calorie restriction or other dietary measures can be therapeutic in MS patients.

a) Piccio LM, Stark JL, Cross AH: Chronic Calorie Restriction Attenuates Experimental Autoimmune Encephalomyelitis. J Leuk Biol 2008; 84:940-948. PMCID: PMC2638732
b) Piccio L, Cantoni C, Ramsbottom M, Mikesell B, Cremasco V, Haynes W, Dong LQ, Chan L, Galimberti D, Cross AH. Lack of adiponectin leads to increased lymphocyte activation and worse severity of a mouse model of multiple sclerosis. Eur J Immunol 2013; 43: 2089-2100. PMCID:PMC3901539

My publications can be found at:
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/47586715/?sort=date&direction=ascending
H-index= 61 (on Google Scholar)

D. Research Support

Ongoing

PO1 NS059560-01 Cross (PI) 10/01/2008 – 04/30/2019
NIH/NINDS
"Biomarkers and pathogenesis of MS: From Mouse to Human"
Goals: This is a Program Project to study diffusion basis spectrum imaging (a type of diffusion imaging) in mouse models and patients with multiple sclerosis. Project 3, of which I am PI, is to cross sectionally and longitudinally assess the various types of MS lesions (T2w, T1w, gad+, black holes). This Project will enroll all clinical subtypes of MS patients
Role: Overall PI of the PPG, and PI of Project 3 and Core A.

Marilyn Hilton Award for Innovation in MS Research Cross (PI) 01/01/15 – 12/31/19
Conrad N. Hilton Foundation
"Use of gradient echo MRI to monitor clinical progression in progressive MS patients"
Goal: This study will determine if gradient echo contrast imaging of brains and upper spinal cords will distinguish progressive MS forms from non-progressive MS forms, and whether it can be used to detect and serve as a biomarker of progression in real time.
Role: PI

RG5979650 (Cross PI) 7/1/2012 – 6/30/2017
National MS Society USA
"Gradient Echo Plural Contrast Imaging to Better Understand MS"
The hypothesis is that GEPCI will measure the extent and severity of *white matter* pathology in MS, resulting in improved correlations with clinical disability and with histopathology, and that phase data will provide new and novel information regarding MS lesion development.

RG4407A2/1 (Cross, Washington Univ site PI. Mowry overall PI) 4/1/13-3/31/17
National MS Society .
"A randomized controlled trial of vitamin D in multiple sclerosis".
This is a prospective, blinded 2-year clinical trial of randomized low versus high dose of oral vitamin D3 given to relapsing-remitting multiple sclerosis patients newly starting glatiramer acetate. No overlap.

SPARC Grant (Yanjiao Zhou PI, A. Cross- co-investigator) 01/01/2015- 12/31/2016
Strategic Pharma-Academic Research Consortium (SPARC)
"Microbiome marker discovery in multiple sclerosis using metagenomic sequencing technology"
Goal of studying the microbiome in MS patients compared with controls

Completed

NIH RO1 NS 051591 / NMSS RG 3915 Voskuhl (PI), Cross (Site PI) **01/12/07 - 04/30/14**

NIH/NINDS and NMSS co-funded
"A Combination Trial of Copaxone Plus Estriol in RRMS"
Goal: This is a placebo controlled, multicenter trial using an estrogen to treat female patients with MS.
Role: Co-Investigator, site PI.

Idea Award **Song (PI)** **10/1/2012 - 9/30/15**
US Department of Defense
"Noninvasive detection and differentiation of axonal injury/loss, demyelination, and inflammation in MS"
Goal: To examine the evolution of corpus callosum de-/re-myelination, and inflammation using in vivo diffusion scanning and immunohistochemistry in mice affected with an animal model of MS - experimental autoimmune encephalomyelitis (EAE).
Role: co-investigator