BIOGRAPHICAL SKETCH

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NAME: Bruce D. Trapp

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

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
Northern Illinois University, DeKalb, Illinois	BS	1972	Experimental Psychology
Loyola University Stritch School of Medicine, Maywood, IL	PHD	01/1977	Anatomy
NIH/NINCDS, Bethesda, Maryland	Postdoctoral Fellow	1984	Neurosciences

A. PERSONAL STATEMENT

A major focus of my laboratory is to understand the pathogenesis of neurological disability in MS patients. We have taken a direct approach to this goal by establishing a rapid autopsy program for MS brains and spinal cords. Several fundamental observations regarding MS pathogenesis have emerged from our studies, including axonal transection in lesions of MS, neuronal mitochondrial changes as a cause of axonal degeneration, the characterization of cortical lesions and associated neuronal/neurite pathology, hippocampal demyelination as a cause of cognitive dysfunction, and the remarkable ability of the MS brain to repair itself. We have been at the cutting edge of MS research for approximately two decades. Our studies take advantage of a large cohort of MS brains and spinal cords that allow state-of-the-art cellular and molecular analysis. These studies are clinically significant because most subpial cortical demyelination occurs without infiltration of peripheral immune cells. Current anti-inflammatory therapies may not reduce subpial demyelination. The characterization of how subpial demyelination occurs, therefore, will help identify novel MS therapies that will delay subpial demyelination.

A second major focus of my lab has been to study hippocampal pathology in postmortem MS brains. We identified the hippocampus as a common site of demyelination and described alterations in neuronal proteins that mediate hippocampal function, memory and learning. These changes in demyelinated hippocampi identify maintenance of synaptic plasticity as a putative therapeutic target for enhancing cognition in MS patients. To extend these postmortem MS hippocampal studies, we have developed a consistent mouse model of hippocampal demyelination that reduces memory and learning and displays similar molecular changes in neuronal proteins as demyelinated MS hippocampi. We take a multidisciplinary approach including electrophysiology, *in vivo* MRI, molecular analysis, and 3D electron microscopy.

1. Trapp BD, Peterson J, Ransohoff RM, Rudick R, Mörk S, et al. Axonal transection in the lesions of multiple sclerosis. N Engl J Med. 1998 Jan 29;338(5):278-85. PubMed PMID: 9445407.
2. Chang A, Tourtellotte WW, Rudick R, Trapp BD. Premyelinating oligodendrocytes in chronic lesions of multiple sclerosis. N Engl J Med. 2002 Jan 17;346(3):165-73. PubMed PMID: 11796850.
3. Dutta R, Chang A, Doud MK, Kidd GJ, Ribaudo MV, et al. Demyelination causes synaptic alterations in hippocampi from multiple sclerosis patients. Ann Neurol. 2011 Mar;69(3):445-54. PubMed PMID: 21446020; PubMed Central PMCID: PMC3073544.

4. Chang A, Staugaitis SM, Dutta R, Batt CE, Easley KE, et al. Cortical remyelination: a new target for repair therapies in multiple sclerosis. Ann Neurol. 2012 Dec;72(6):918-26. PubMed PMID: 23076662; PubMed Central PMCID: PMC3535551.

B. POSITIONS AND HONORS

Positions and Employment

1984 – 1988	Assistant Professor of Neurology, Johns Hopkins University, School of Medicine, Baltimore, MD
1988 – 1994	Associate Professor of Neurology, Johns Hopkins University, School of Medicine, Baltimore, MD
1994 -	Chairman, Department of Neurosciences, Cleveland Clinic, Lerner Research Institute, Cleveland, OH
1995 -	Professor, Department of Neurosciences, Case Western Reserve University, Cleveland, OH
2003 -	Professor, Cleveland Clinic Lerner College of Medicine at CWRU, Cleveland, OH

Other Experience and Professional Memberships

2008 -	Fellow, American Association for the Advancement of Science

Honors

1985	Jordi Folch-Pi Award, American Society of Neurochemistry
1986	Weil Award, American Association of Neuropathologists
1986	Harry Weaver Neuroscience Scholar, National Multiple Sclerosis Society (NMSS)
2002	Jacob Javits Award in Neurosciences, NIH/NINDS
2003	John Dystel Prize for Multiple Sclerosis Research, American Academy of Neurology and NMSS
2007	Reason for Hope Award, Zinken Charitable Foundation
2009	Stephen C. Reingold Research Award, NMSS
2013	Volunteer Hall of Fame for Scientific Researchers, NMSS

C. CONTRIBUTIONS TO SCIENCE

1. My most seminal contribution to science is the characterization of axonal transection in multiple sclerosis (MS) brains. Traditionally, it had been assumed that the MS disease process spared axons. Thus, major therapeutic and research efforts had been directed toward limiting immune-mediated damage to myelin and promoting remyelination. However, we and others have established that axonal injury in MS causes permanent neurologic disability. Our results firmly established that axonal transection is a consistent consequence of demyelination in the brains of patients with MS. Axonal transection, synaptic plasticity, and neuronal degeneration are the pathological correlates of irreversible neurologic disability in MS patients. The original publication establishing these findings in the *New England Journal of Medicine* (a) is the most cited primary research article in MS research.
   a. **Trapp BD**, Peterson J, Ransohoff RM, Rudick R, Mörk S, Bö L. 1998. Axonal transection in the lesions of multiple sclerosis. *N Engl J Med.* 338(5):278-85. PMID: 9445407
   b. **Trapp BD**, Ransohoff R, Rudick R. 1999. Axonal pathology in multiple sclerosis: relationship to neurologic disability. *Curr Opin Neurol.* 12(3):295-302. PMID: 10499174
   c. Bjartmar C, Kidd G, Mörk S, Rudick R, **Trapp BD**. 2000. Neurological disability correlates with spinal cord axonal loss and reduced N-acetyl aspartate in chronic multiple sclerosis patients. *Ann Neurol.* 48(6):893-901. PMID: 11117546
   d. **Trapp BD**, Nave KA. Multiple sclerosis: an immune or neurodegenerative disorder? 2008. *Annu Rev Neurosci.* 31:247-69. PMID: 18558855
2. Generation and differentiation of new oligodendrocytes in demyelinated white matter is the best described repair process in the adult human brain. However, remyelinating capacity falters with age in patients with MS. We established that premyelinating oligodendrocytes are present in chronic white matter lesions in MS brains. These results indicate that remyelination is not limited by an absence of oligodendrocyte progenitors, or by their failure to generate oligodendrocytes. Thus, understanding the cellular interactions between premyelinating oligodendrocytes, axons, and the microenvironment of MS lesions may lead to

effective strategies for enhancing remyelination. We have further established that endogenous remyelination of the cerebral cortex occurs in individuals with MS regardless of disease duration or chronological age. This is critically important, because it opens the door for cortical remyelination to be considered as a primary outcome measure in clinical trials testing remyelination therapies.

a. Chang A, Nishiyama A, Peterson J, Prineas J, **Trapp BD**. 2000. NG2-positive oligodendrocyte progenitor cells in adult human brain and multiple sclerosis lesions. *J Neurosci.* 20(17):6404-12. PMID: 10964946

b. Chang A, Tourtellotte WW, Rudick R, **Trapp BD**. 2002. Premyelinating oligodendrocytes in chronic lesions of multiple sclerosis. *N Engl J Med.* 346(3):165-73. PMID: 11796850

c. Chang A, Smith MC, Yin X, Fox RJ, Staugaitis SM, **Trapp BD**. 2008. Neurogenesis in the chronic lesions of multiple sclerosis. *Brain* 131(Pt 9):2366-75. PMID: 18669500; PMCID: PMC2525445

d. Chang A, Staugaitis SM, Dutta R, Batt CE, Easley KE, Chomyk AM, Yong VW, Fox RJ, Kidd GJ, **Trapp BD**. 2012. Cortical remyelination: a new target for repair therapies in multiple sclerosis. *Ann Neurol.* 72(6):918-26. PMID: 23076662; PMCID: PMC3535551

3. We have also described gray matter demyelination in MS brains. We described 3 distinct patterns of cortical demyelination in MS brains. Leukocortical lesions are contiguous with subcortical white matter lesions. Intracortical lesions are small, confined to the cortex, and are often perivascular. Subpial lesions extend from the pial surface to cortical layer III or IV. These data support the concept that cortical demyelination is a major cause of neurological dysfunction in MS patients. We also described demyelination and neuronal pathology in the hippocampus. Over 50% of MS patients demonstrate memory impairments, and the molecular basis of this memory dysfunction has not yet been established.

a. Peterson JW, Bö L, Mörk S, Chang A, **Trapp BD**. 2001. Transected neurites, apoptotic neurons, and reduced inflammation in cortical multiple sclerosis lesions. *Ann Neurol.* 50(3):389-400. PMID: 11558796

b. Bø L, Vedeler CA, Nyland HI, **Trapp BD**, Mørk SJ. 2003. Subpial demyelination in the cerebral cortex of multiple sclerosis patients. *J Neuropathol Exp Neurol.* 62(7):723-32. PMID: 12901699

c. Dutta R, Chang A, Doud MK, Kidd GJ, Ribaudo MV, Young EA, Fox RJ, Staugaitis SM, **Trapp BD**. 2011. Demyelination causes synaptic alterations in hippocampi from multiple sclerosis patients. *Ann Neurol.* 69(3):445-54. PMID: 21446020; PMCID: PMC3073544

d. Dutta R, Chomyk AM, Chang A, Ribaudo MV, Deckard SA, Doud MK, Edberg DD, Bai B, Li M, Baranzini SE, Fox RJ, Staugaitis SM, Macklin WB, **Trapp BD**. 2013. Hippocampal demyelination and memory dysfunction are associated with increased levels of the neuronal microRNA miR-124 and reduced AMPA receptors. *Ann Neurol.* 73(5):637-45. PMID: 23595422; PMCID: PMC3679350

4. Another focus in my lab is the role of axonal mitochondria pathology in MS and inherited diseases of myelin. We reported reductions in 26 nuclear-encoded mitochondrial genes in demyelinated MS motor cortex. While this paper supported the concept that mitochondrial dysfunction was a major contributor to axonal degeneration in MS lesions, little was known about axonal mitochondria. Therefore, we investigated axonal mitochondria in organotypic slice cultures and identified two mitochondrial populations: the majority (>90%) were large and stationary, while the remaining 10% were small and motile. We reported that stationary mitochondria are relatively stable axonal structures in myelinated, demyelinated, and remyelinated axons and that motile mitochondria sustain stationary mitochondrial turnover and redistribution through fission and fusion. Stationary mitochondrial volume is dynamically increased by demyelination and is significantly decreased by remyelination. By adjusting the size of stationary mitochondria, axons dynamically regulate ATP production to meet the energy demands of nerve conduction. Furthermore, we have shown juxtaparanodal enrichment of stationary mitochondria and neuronal activity-dependent dynamic modulation of mitochondrial distribution and transport in nodal axoplasm. We also reported that syntaphilin-mediated immobilization of mitochondria to microtubules is required for mitochondrial volume increases following acute demyelination and that this immobilization protects against axonal degeneration.

a. Dutta R, McDonough J, Yin X, Peterson J, Chang A, Torres T, Gudz T, Macklin WB, Lewis DA, Fox RJ, Rudick R, Mirnics K, **Trapp BD**. 2006. Mitochondrial dysfunction as a cause of axonal degeneration in multiple sclerosis patients. *Ann Neurol.* 59(3):478-89. PMID: 16392116

a. **Trapp BD**, Stys PK. 2009. Virtual hypoxia and chronic necrosis of demyelinated axons in multiple sclerosis. *Lancet Neurol.* 8(3):280-91. PMID: 19233038

c. Ohno N, Kidd GJ, Mahad D, Kiryu-Seo S, Avishai A, Komuro H, **Trapp BD**. 2011. Myelination and axonal electrical activity modulate the distribution and motility of mitochondria at CNS nodes of Ranvier. *J Neurosci*. 31(20):7249-58. PMID: 21593309; PMCID: PMC3139464

d. Ohno N, Chiang H, Mahad DJ, Kidd GJ, Liu L, Ransohoff RM, Sheng ZH, Komuro H, **Trapp BD**. 2014. Mitochondrial immobilization mediated by syntaphilin facilitates survival of demyelinated axons. *Proc Natl Acad Sci U S A.* 111(27):9953-8. PMID: 24958879; PMCID: PMC4103317

5. A further area of interest in my lab is correlations between MS brain magnetic resonance imaging (MRI) abnormalities and tissue pathology. Magnetic resonance imaging (MRI) is the most commonly used tool for diagnosis and monitoring of MS. Because of its high sensitivity, MRI is an invaluable method for following the subclinical progression of the disease. Unfortunately, conventional MRI is limited by its low pathological specificity. We have established a unique rapid autopsy program for procurement of MS brains and spinal cord. MS patients followed at the Cleveland Clinic Mellen Center prospectively sign-up for the donation. Upon death, their corpse is transported by ambulance to the Mellen Brain Imaging Center. Two hours of standard and advanced brain imaging is performed on the brain *in situ*. The corpse is then transported to pathology where the brain and spinal cord are removed and placed in fixative. MRI abnormalities are co-registered with the brain slices and regions of interest (ROIs) are removed and characterized by immunocytochemistry. We have shown that only 55% of ROIs with increased T2 densities are demyelinated. If a ROI is abnormal by T1, T2, and MTR, 83% are demyelinated. These data establish that MRI is moderately successful at detecting brain white matter demyelination. In ROIs that were demyelinated, axonal swelling and axonal loss were major pathological features that distinguish T2T1MTR regions from T2-only regions.

a. Fisher E, Chang A, Fox RJ, Tkach JA, Svarovsky T, Nakamura K, Rudick RA, **Trapp BD**. (2007) Imaging correlates of axonal swelling in chronic multiple sclerosis brains. *Ann Neurol* 62:219-28. PMID: 17427920

b. Young EB, Fowler CD, Kidd GJ, Chang A, Rudick RA, Fisher E, **Trapp BD**. (2008) Imaging correlates of decreased axonal Na+/K+ ATPase in chronic MS lesions. *Ann Neurol* 63:428-35. PMID: 18438950

c. Moll NM, Cossoy MB, Fisher E, Staugaitis SM, Tucky BH, Rietsch AM, Chang A, Fox RJ, **Trapp BD**, Ransohoff RM. (2009) Imaging correlates of leukocyte accumulation and CXCR4/CXCL12 in multiple sclerosis. *Arch Neurol* 66:44-53. PMID: 19139298; PMCID: PMC2792736

d. Chen JT, Easley K, Schneider C, Nakamura K, Kidd GJ, Chang A, Staugaitis SM, Fox RJ, Fisher E, Arnold JL, **Trapp BD**. (2013) Clinically feasible MTR is sensitive to cortical demyelination in MS. Neurology 80:246-52. PMID: 23269598; PMCID: PMC3589181

D. RESEARCH SUPPORT

Ongoing Research Support

Pathogenesis of Neurological Disability in Primary Diseases of Myelin
R35 NS097303 NINDS 12/01/2016-11/30/2024 TRAPP, BRUCE (PI)
In this proposal, we will address three key questions: 1) How does myelin provide trophic support to axons? 2) How does demyelination affect neurons and their synaptic connections? 3) How does subpial cortical demyelination occur?

R01 MH099588 NIMH 01/15/2013-11/30/2018 TRAPP, BRUCE (PI)
New Models for Astrocyte Function in Genetic Mouse Models of Autism Spectrum Disorders
These studies will elucidate roles of astrocytes in ASDs and will provide a critical genetic and ultrastructural framework for the development of future therapeutic strategies that target astrocyte function. This grant is in a no-cost extension.

Genzyme GENZ1502BT 02/01/2015-01/31/2020 TRAPP, BRUCE (PI)
Rapid Autopsy Program at the Cleveland Clinic Foundation
This supports our Rapid Autopsy Tissue Acquisition Program to collect postmortem brain and spinal samples from patients with multiple sclerosis and Alzheimer's disease.

TECG20150141, Ohio Third Frontier 12/01/2014-12/01/2018 TRAPP, BRUCE (PI)
Cleveland Clinic Rodent Imaging Center
This grant from the State of Ohio was to develop a rodent MRI facility at the Lerner Research Institute. The Trapp lab does not receive any operating costs from this grant and it is in a no-cost extension.

ALS Association RG 01/01/2016-12/31/2018 TRAPP, BRUCE (Co-PI)
Postmortem MRI and pathology in ALS patients to identify biomarkers and evidence of oligodendrocyte dysfunction
The overall goal of this project is to identify magnetic resonance imaging (MRI) biomarkers of ALS CNS pathology and determine if the pathology features dysfunctional oligodendrocytes.

R21 NS099734 08/15/2017-07/31/2019 JEHI, LARA (PI)
Abnormal Interleukin 1-B inflammasome activation and epilepsy surgery outcomes
Role: Co-Investigator
This project explores the central hypothesis that genetic variability in IL-1β and its related inflammasome translates into an altered pattern of microglial activation after epilepsy surgery, facilitating subsequent epileptogenesis in brain tissue at the edge of the resection and later seizure recurrence.