BIOGRAPHICAL SKETCH

NAME: **Ranjan Dutta, Ph.D.**

eRA COMMONS USER NAME: **DUTTAR**

POSITION TITLE: **Assistant Professor, Molecular Medicine/ Assistant Staff**

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	Start Date MM/YY	FIELD OF STUDY
Calcutta University, India	B.S.	03/1991	Chemistry
Calcutta University, India	M.S.	10/1993	Biochemistry
Department of Life Science & Biotechnology, Jadavpur University, India	Ph.D.	01/1996	Human Genetics
Department of Neurosciences, Cleveland Clinic	Postdoctoral Fellow	09/2002	Neuroscience
Department of Neurosciences, Cleveland Clinic	Research Associate	10/2006	Neuroscience

A. Personal Statement

The major goal of our research is to investigate the pathogenesis of neurological disability in the demyelinating disease, multiple sclerosis (MS). We use several methods to investigate the role of glial cells during demyelination and remyelination. Two major factors underlie the progressive disability in MS patients, neuro-axonal loss following demyelination and remyelination failure. To shorten the translation redundancy, we take a 'reverse approach' where histopathology/molecular changes in MS brains are replicated in vitro and animal models. Several fundamental observations regarding MS pathogenesis have emerged from our studies, including neuronal mitochondrial changes as a cause of axonal degeneration as well as hippocampal demyelination as a cause of cognitive dysfunction. We have been at the cutting edge of MS research in identification of neuronal microRNAs that regulate neuronal gene expression following demyelination. Our current investigation includes glial pathology and difference in remyelination efficiency in progressive MS using a combination of histopathology, molecular and epigenetic markers in MS brains, in vitro and animal models and single cell approaches. Our laboratory has significant role in maintain a raid autopsy program for MS brain donation and subsequent research.

Ajai Tripathi, Christina Volsko, Jessie P. Garcia, Eneritz Agirre, Kevin C. Allan, Paul J. Tesar, Bruce D. Trapp, Goncalo Castelo-Branco, Fraser J. Sim, Ranjan Dutta. (2019). Oligodendrocyte intrinsic miR-27a controls myelination and remyelination. *Cell Reports.* 29(4):904-919. PMID: 31644912; PMCID: PMC6874400.

Dutta R, Mahajan K, Nakamura K, Ontaneda D, Chen J, Dudman J, Volsko C, Dunham J, Fox R and Trapp B. (2019). Comprehensive Autopsy Program for Individuals with Multiple Sclerosis. *Journal of Visual Experimentation*. 19: (149-155). PMID: 31380830.

B. Positions and Honors

Professional Experience:

2009 - 2012 Project Staff, Department of Neurosciences, Cleveland Clinic, OH
2009 - Instructor, Department of Biological Sciences, Cleveland State University
2012 - Staff Scientist; Department of Neuroscience, Cleveland Clinic, OH
2016 - Assistant Staff/Assistant Professor Department of Neuroscience, Cleveland Clinic, OH

Teaching:

2009 - Genetics: Department of Biological Sciences, Cleveland State University

Honors and other professional activities:

1996 - 2000 Ministry of Home Affairs, Govt of India, fellowship for Doctoral work.
2001 Indian Science Congress 'Young Scientist Award'.
2005 American Society of Neurochemistry, "Young Investigator Educational Award".
2005 - Member American Society of Neurochemistry
2006 - Member Society for Neuroscience
2006 - Member American Society of Human Genetics
2011-2013 Member, IPMSC Working Group "Target/pathways identification and Validation / repurposing of existing therapeutic agents".
2012 Poster Presentation Award, ECTRIMS, Lyon
2017 - Member American Academy of Neurology
2017 - Editorial Board member, Multiple Sclerosis Journal
2019 - Editorial Board member, Scientific Reports

Grant Reviewer:

2010-2014 Pilot Grant Reviewer, National MS Society, USA (Glial Biology Study Section)
2011- 2015 The Wellcome Trust, UK, (Neurobiology and Glial biology)
2014 - 2019 Neurological Foundation of New Zealand
2014 - 2019 MS Research Council Australia
2015 - 2019 MS Research Council Netherlands
2016 - 2019 Grant Reviewer, National MS Society, USA (Biomedical Section A)
2016- 2019 MS Research Council UK
2016- NINDS/NIH, Clinical Neuroimmunology and Brain Tumors [CNBT]/ ADHOC
2018- NINDS/NIH Special Emphasis Panel ZRG1 BDCN-G 03 M: Neuroimmunology, Neuroinflammation, and Brain Tumor/ ADHOC
2019- NINDS/NIH: Fellowship F01B: Learning and Memory, Language, Communication and Related Neurosciences
2018-2019 LRI Internal Funding Review Committee (IFRC)

Journal Reviewer:

Neurology, Annals of Neurology, Brain, Journal of Neuroscience, Journal of Neuropathology and Experimental Neurology, Multiple sclerosis Journal, ASN Neuro, Neurochemistry International, Journal of Neuroscience Research, American Journal of Neuroscience Research, Acta Neuropathologica, Journal of Neurochemistry, MicroRNA, MS Translational Neurology, Expert Review on Therapeutics, Scientific Reports, FASEB

C. Contributions to Science

1. Regulators of myelination / remyelination in MS

Remyelination is considered to be one of the major neuroprotective mechanisms in MS brains. Studies have shown that remyelination is not limited due to absence of oligodendrocyte progenitors, but rather because of failure to mature into adult oligodendrocytes. One of the major focuses of our studies has been to understand why remyelination fails in MS brains. Using both human MS brains and animal models, we identified genes and epigenetic modifiers that act as inhibitors to halt remyelination.

a) 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.
b) Bai CB, Sun S, Roholt A, Benson E, Edberg D, Medicetty S, Dutta R, Kidd G, Macklin WB, Trapp B. (2017). A mouse model for testing remyelinating therapies. *Exp. Neurol.*:283(A):330-340. PMID: 27384502; PMCID: PMC520734.
c) Leslie Kirby, Jing Jin, JG Cardona, Matthew Smith, Kyle Martin, Jingya Wang, Hayley Strasburger, Leyla Herbst, Maya Alexis, Jodi Karnell Todd Davidson, Ranjan Dutta, Joan Goverman, Dwight Bergles and Peter A. Calabresi. (2019). Oligodendrocyte Precursor Cells Present Antigen and are Cytotoxic Targets in Inflammatory Demyelination. *Nature Communications.* 10(1):3887-3407. PMID: 31467299; PMCID: PMC6715717.
d) Darpan Saraswat, Jessie Polanco, HJ Shayya, Ajai Tripathi , RR Welliver, S U Pol, J E Broome, M A O'Bara, T H. van Kuppervelt, J J Phillips, Ranjan Dutta, Fraser J. Sim. 2020. Overcoming the inhibitory microenvironment surrounding oligodendrocyte progenitor cells following demyelination. *Biorxiv. https://doi. org /10.1101 /2020.01.21.906073 (Under Review)*.

2. MicroRNAs and other epigenetic modifiers affecting cellular changes in the CNS

Major focus of our studies has been to determine the regulatory mechanisms that control gene and protein expression in MS brains. We specifically focused on the role of epigenetic modifiers and their cellular localization. We identified neuronal microRNAs altered in the hippocampus following demyelination and their correlation with memory loss. Our collaborative studies have also identified several DNA methylation sites in MS brains using comparative profiling of normal white matter tissues. We have also used our approach to identify novel functions of activated microglial cells in the CNS and how they alter neurogenesis and facilitate neuroprotection.

a) 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.
b) Huynh JL, Garg P, Thin TH, Yoo S, Dutta R, Trapp BD, Haroutunian V, Zhu J, Donovan MJ, Sharp AJ, Casaccia P. (2014) Epigenome-wide differences in pathology-free regions of multiple sclerosis-affected brains. *Nature Neuroscience* 17(1):121-30. PMID: 24270187; PMCID: PMC3934491.
c) Chomyk A, Volsko C, Tripathi A, Deckard S, Trapp B, Fox R and Dutta R. (2017). DNA methylation in demyelinated multiple sclerosis hippocampus. *Scientific Reports. 18 7(1):8696-8705*. PMCID: 5562763.
d) Tripathi A, Volsko C, Datta U, Regev K and Dutta R. (2019). Expression of disease-related miRNAs in white matter lesions of progressive multiple sclerosis brains. *Annals of Clinical and Translational Neurology*. 6(5):854-862. PMID: 31139683. PMCID: PMC6530016.

3. Role of microglial cells in CNS diseases

Our laboratory has been interested in studies using postmortem MS brains to understand role of glial cells in multiple sclerosis and other CNS diseases. We used both genomic and proteomic approaches to detect to identify the functional changes in glial cells following activation as well as demyelination. Our recent studies have shown significant differences in the synaptic arrangement, structures of synaptic boutons, microglial cells as well as abberant myelination in animal models of ASD.

a) Chen Z, Jalabi W, Hu W, Park HJ, Gale JT, Kidd GJ, Bernatowicz R, Gossman ZC, Chen JT, Dutta R, Trapp BD. (2014) Microglial displacement of inhibitory synapses provides neuroprotection in the adult brain. *Nature Communications* 5:4486-89. PMID: 25047355; PMCID: PMC4109015.
b) Savarin C, Dutta R, Bergmann C. (2018). Distinct gene profiles of bone marrow-derived macrophages and microglia during neurotropic coronavirus-demyelination. *Frontiers in Immunology.*11;9:1325. PMID: 29942315; PMCID: PMC6004766.
c) Kremer D, Gruchot J, Weyers V, Oldemeier L, Göttle P, Healy L, Ho Jang J, Kang T Xu Y, Volsko C, Dutta R, Trapp BD, Perron H, Hartung HP, Küry P. 2019. pHERV-W envelope protein fuels microglial cell-dependent neurodegeneration. *Proc Natl Acad Sci USA.* (2019). 116(30):15216-15225. PMID: 31213545. ; PMCID: PMC6660731.
d) Nicholas Sarn, Ritika Jaini, Stetson Thacker, Hyunpil Lee, Ranjan Dutta, Charis Eng. (2020). Decreased near Pten Increases Microglial Activation and Synaptic Pruning in a Murine Model with Autism-Like Phenotype. *Molecular Psychiatry (In Press).*

4. Axonal and neuronal loss in neurodegenerative disease

Neuronal and axonal loss are considered to be primary reasons for the continuous neurological decline observed in progressive MS patients. Using MS postmortem tissues, we were the first to report changes in nuclear encoded mitochondrial genes in MS cortex. This has been one of the most cited research communications in the field, which provides a mechanism of axonal degeneration in MS. We have also been involved in collaborative efforts to determine the role of glial cells in neuronal protection in stoke and autism spectrum disorders.

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.
b) 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.
c) Bastian C, Quinn J, Tripathi A, Danielle A, McCray A, Dutta R, Baltan S and Brunet S (2019). CK2 inhibition confers functional protection to young and aging axons against ischemia by differentially regulating the CDK5 and AKT signaling pathways. *Neurobiology of Disease.* (18)30149-9. PMID: 29944965.
d) Lee H, Thacker S, Sarn N, Dutta R and Eng C. (2019). Constitutional mislocalization of Pten drives precocious maturation in oligodendrocytes and aberrant myelination in model of autism spectrum disorder. *Translational Psychiatry*. (9) 13-25.PMID:30664625; PMCID: PMC6341090.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/141ghFAGNhEQQ/bibliography/45988319/public/?sort=date&direction=descending

D. Additional Information: Research Support

ACTIVE

MicroRNAs as critical regulators of remyelination in MS
R01 NS096148 PI: Ranjan Dutta 05/11/2016 to 02/28/2021
Funding Agency: NIH/NINDS
Studies outlined in this proposal investigates role of miRNAs identified in MS brains in their ability to modulate remyelination efficiency.

Pathogenesis of Neurological disability in primary diseases of myelin
R35 NS097303 PI: Bruce D. Trapp 07/01/2016 to 06/30/2024
Funding Agency:NIH Role: Co-I
Key personnel in NINDS outstanding investigator award to investigate the pathogenesis of myelin diseases.

PENDING

Disruption of circadian rhythm as a mechanism underlying impaired repair in MS
Grant mechanism: MPI/RO1 PI: Ranjan Dutta/Sujata Rao 07/01/2020 to 06/30/2025
Funding Agency: NIH
The goal of this grant is to understand the role of circadian rhythm in repair in multiple sclerosis patients.

Thalamic degeneration as window into the pathogenesis of multiple sclerosis
Grant mechanism: MPI/RO1 PI: Ranjan Dutta/Dan Ontaneda 07/01/2020 to 06/30/2025
Funding Agency: NIH
The goal of this grant is to understand the role of thalamic degeneration in multiple sclerosis patients.

Pathological and Molecular correlate of primary neurodegeneration in Multiple Sclerosis
Funding Agency: NMSS PI: Ranjan Dutta 10/01/2020 to 09/30/2023
The goal of this grant is to understand the molecular pathways operating in thalamic region of MS patients.

Dissecting the role of astrocytes in Pten-associated autism spectrum disorder
Grant mechanism: MPI/RO1 PI: Charis Eng/ Ranjan Dutta 12/01/2020 to 11/30/2025
Funding Agency: NIH
The goal of this grant is to understand the role of astrocytes in autism spectrum disorder.

COMPLETED within last 3 years

Pathogenesis of cortical demyelination in progressive multiple sclerosis
RG 5298-A PI: Ranjan Dutta 04/01/2015 to 10/03/2018
Funding Agency: NMSS, USA
The proposed study compares cortical pathology and neuronal changes in primary progressive MS patients.

Identification of Novel MicroRNAs in white matter lesions from MS Patients
RG4280-B2 PI: Ranjan Dutta 07/01/2012 to 06/31/2015
Funding Agency: NMSS, USA
This grant is a competetive renewal of RG4280-A investigating microRNAs that are altered in MS lesions.