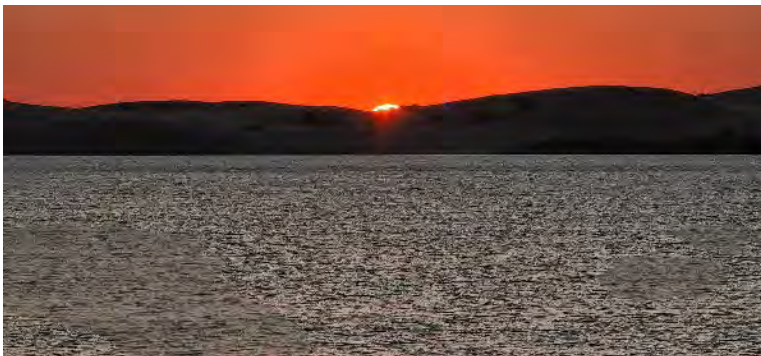
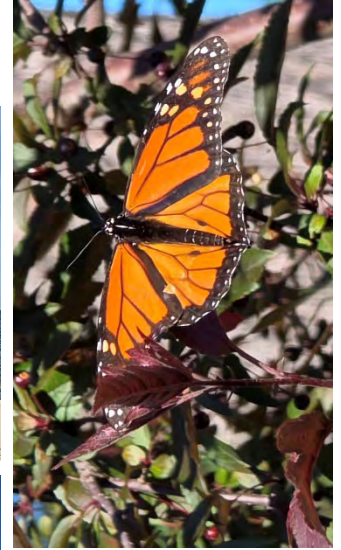


The 15th Great Lakes Glia Conference



October 11th- 13th, 2026
Park Place Hotel & Conference Center
Traverse City, MI
<http://www.greatlakesglia.org>

Great Lakes Glia 2026

Park Place Hotel & Conference Center - Traverse City, MI

<http://www.greatlakesglia.org>

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A Familiar Damselfly from Mackinaw Island, but equally at home in Grosse Pointe back yards (Alex Gow)

Empire beach, looking out at Lake Michigan (Pam Knapp)

Monarch butterfly resting in a crab apple tree, Detroit (Alex Gow)

Second row left to right (submitted by)

The wagon of pumpkins in the Traverse City downtown farmer's market (Saturdays!) (Pam Knapp)

Point Betsie Lighthouse, Benzie County (Pam Knapp)

Red poppy, Mackinaw Island (Alex Gow)

Third row left to right (submitted by)

Whitefish boats on canal, Leland, MI, home of The Cove restaurant and the "Chubby Mary" (Pam Knapp)

Sunset over Silver Lake, Silver Lake State Park, Mears (Alex Gow)

View from the Top of the Park, Park Place Hotel, Traverse City (Pam Knapp)

Great Lakes Glia 2026

Park Place Hotel & Conference Center - Traverse City, MI

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We gratefully acknowledge the generous support of the following sponsors. Their commitment to Great Lakes Glia is vital to the success of this event.



Please join the Great Lakes Glia scientific conference and the Alzheimer's Association

Community and Caregiver Support Day

Sunday October 11, 2026 from 1-3 PM

Park Place Hotel
300 E. State Street
Traverse City, MI 49684

Program:

1-1:30 pm **Dr. Linda Van Eldik**, Director,
Kentucky Alzheimer's Disease Research Center
Blood-based biomarkers for Alzheimer's disease

1:30-2 pm **Dr. David Morgan**
Michigan State University Foundation Professor
and Director, Alzheimer's Alliance
The history of immunotherapy as the first disease modifying treatment for Alzheimer's disease

2-2:30 pm **Kristen Erby Weber**
Regional Director Northern Michigan
Alzheimer's Association
Communication Strategies for Caregivers

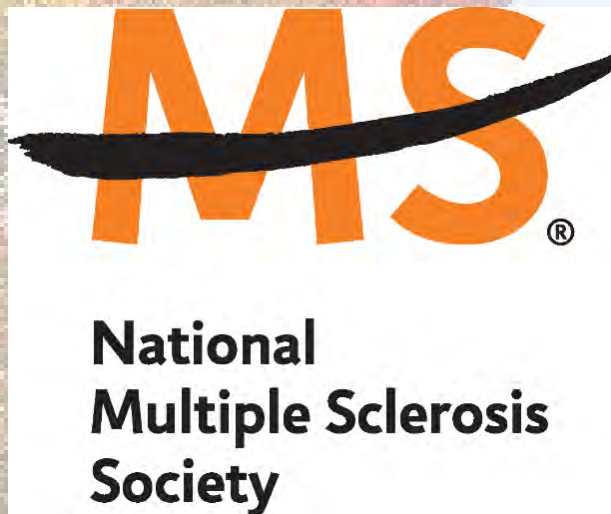
2:30-3 pm **Q&A with Speaker Panel**

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Call for Papers

Measuring Myelin Integrity: Coming of Age in Preclinical and Clinical Arenas

An Article Collection appearing in

ASN Neuro



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November 1st, 2026

Guest Advisors:

Prof. Alexander Gow
*Wayne State University,
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Prof. Nikola Stikov
*University of Montreal,
Quebec, Canada*



Contact Krista Thom
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for more information.

https://think.taylorandfrancis.com/article_collections/measuring-myelin-integrity-coming-of-age-in-preclinical-and-clinical-arenas/

Great Lakes Glia 2026

Park Place Hotel & Conference Center - Traverse City, MI

<http://www.greatlakesglia.org>

Program

Sunday, October 11

1:00 pm – Premeeting Open Public Forum: Alzheimer’s Disease

Grandview I

Chair: Marcia Gordon, Michigan State University

- Linda J. Van Eldik (University of Kentucky) – Blood-based biomarkers for Alzheimer’s disease
- David Morgan (Michigan State University) – The history of immunotherapy as the first disease modifying treatment for Alzheimer’s disease
- Kristen Erby Weber (Northern Michigan Alzheimer’s Association) – Communication Strategies for Caregivers
- Q & A with speaker panel

4:30 pm – Opening Reception

Top of the Park

6:00 pm – Dinner (Top of the Park)

7:30 pm – Session 1: Activation of Inflammatory Pathways in ALS

Grandview I

Chair: Douglas Feinstein, University of Illinois – Chicago

- Daryl Bosco (University of Massachusetts) – *Investigating the effects of ALS-linked mutations on intrinsic properties of microglia*
- Fei Song (University of Illinois, Chicago) – *Therapeutic targeting of neuregulin signaling in ALS and Alzheimer’s disease: Implications for neuroinflammation and neurodegeneration*
- Allison Ebert (Medical College of Wisconsin) – *Activation of inflammatory pathways in ALS*
- 10-minute talk (Student/Postdoc selected from abstracts)

Monday, October 12

8:00 am – Breakfast

Top of the Park

8:45 am – KEYNOTE PRESENTATION

Grandview I

Speaker: Linda J. Van Eldik, University of Kentucky

Discovery of Small Molecule Therapeutic Candidates That Target Dysregulated Neuroinflammation in Alzheimer's Disease

9:45 am – Break

10:00 am – Poster Blitz: 2-minute Student/Postdoc presentations

Grandview I

10:30 am – Session 2: Microglia and Resilience in Alzheimer's Disease

Grandview I

Chair: Marcia Gordon, Michigan State University

- David G Morgan (Michigan State University) – *Innate immune activation in Alzheimer's disease pathology*
- Shannon Moore (University of Michigan) – *Signatures of resilience to cognitive decline in an Alzheimer's disease mouse model*
- Colleen Zaccard (Northwestern University) – *Inflammation-driven tunneling nanotubes in microglia-synapse crosstalk and neurodegenerative disease*
- Sarah Elzinga (Michigan State University) – *Neuroinflammation and senescence contribute to cognitive impairment in mouse and man*

Noon – Free Time

3:00 pm – Poster Session

Grandview II

4:30 pm – Session 3: Glial Function and Dysfunction in Neurological Disease

Grandview I

Chair: Matthew Benskey, Michigan State University

- Matthew Benskey (Michigan State University) – *Investigating the role of the complement system in the glial response in synucleinopathy*
- Douglas Feinstein (University of Illinois at Chicago) – *Astrocyte metabolic dysfunction increases ferroptosis and contributes to oligodendrocyte death*
- Hayley McLoughlin (University of Michigan) – *Glial cells in poly-glutamine movement disorders*
- 10-min talk (Student/Postdoc selected from abstracts)

7:00 pm – Dinner

Top of the Park

8:30 pm – Poster Session & Refreshments

Grandview II

Tuesday, October 13

7:30 am – Breakfast

Top of the Park

8:15 am – KEYNOTE PRESENTATION

Grandview I

Speaker: *Dwight Bergles, Johns Hopkins University*

Wrapping the Brain: How Myelin is Generated Across Space and Time

9:15 am – Poster award announcements

9:20 am – Break

**9:30 am – Session 4: Non-Invasive Assessment of Myelin Integrity
in CNS Diseases**

Grandview I

Chair: *Alexander Gow, Wayne State University*

- Evan Malin (Wayne State University) – *Exploiting MR relaxation phenomena to advance the understanding of white matter microvasculature: its application to development/aging and psychiatric disorders*
- Mariana Lazar (New York University) – *MRI methods for myelin and g-ratio mapping and their application to neuropsychiatric disorders and aging*
- Nikola Stikov (Montreal Heart Institute – NeuroPoly) – *In vivo imaging of the myelin g-ratio*
- Alexander Gow (Wayne State University) – *Accurate myelin g ratios from electron microscopy to calibrate MR studies*

11:30 am – Lunch Break-out

Grandview I

**12:00 pm – Session 5: Astrocyte Biology Across Multiple Scales
of Physiology and Pathology**

Grandview I

Chair: *Maurizio De Pitta, Krembil Brain Institute*

- Alex Dranovsky (Columbia University) – *Astrocytes as orchestrators of hippocampal function*
- Maryam Faiz (University of Calgary) – *The gut microbiota as a modulator of astrocyte state in health and disease*
- Annalisa Scimemi (SUNY – Albany) – *Glutamate spillover sharpens spatial representations in hippocampal area CA1*
- 10-min talk (Student/Postdoc selected from abstracts)

2:00 pm – End of Meeting

Abstracts

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Standardized Where It Matters, Adaptive Where It Helps: MyeliMetric-V2 for Myelin G-Ratio Analysis

Intakhar Ahmad^{1,2}, Farjana Sultana Chowdhury³, Anne I. Boullerne^{1,2}, Alexander Gow⁴, Douglas L. Feinstein^{1,2}

¹ Department of Anesthesiology, University of Illinois Chicago, Chicago, IL, USA. ² Jesse Brown VA Medical Center, Chicago, IL, USA. ³ Western Norway University of Applied Sciences, Bergen, Norway. ⁴ Wayne State University School of Medicine, Detroit, MI, USA.

Quantitative myelin g-ratio analysis is widely used to assess oligodendrocyte and myelin injury, demyelination, and repair. However, fixed analysis settings can be difficult to apply across tissues, disease models, and image-analysis pipelines. We previously developed MyeliMetric, a python-based platform to automate g-ratio analysis using a binning approach. MyeliMetric-V2 extends the published MyeliMetric framework by preserving standardized computational definitions while allowing investigators to adapt biologically relevant analysis choices to their own experiments.

The central advance in V2 is flexibility within a standardized workflow. Users can choose the number of fiber-diameter bins, modify minimum axon and myelin exclusion thresholds, and analyze either Excel or CSV datasets, while retaining the published defaults when desired. Fiber-diameter ranges are now derived from pooled control animals rather than the first control animal loaded, reducing dependence on sample order. V2 also provides a standalone Windows application that requires no separate Python installation, a simplified three-step workflow, automatic Control/Experimental/Summary output folders, activity logging, and an exclusion audit that records filtered measurements.

We tested whether this added flexibility altered the validated computational behavior. Using synthetic data with imposed control and experimental g-ratios of 0.70 and 0.80, MyeliMetric-V2 recovered 0.704 and 0.800, respectively. Analysis of previously characterized experimental data produced grand g-ratios of 0.784 and 0.778, agreeing with published values within 0.01. Changing bin number and exclusion thresholds produced the expected changes in stratification and filtering without altering the core g-ratio calculation.

By separating fixed computational principles from user-adjustable analytical choices, MyeliMetric-V2 provides glial researchers with a standardized yet adaptive approach for quantifying global and caliber-specific changes in axon-myelin integrity across studies of myelin injury and repair.

MyeliMetric-V2 website: <https://intakhar-ahmad.github.io/MyeliMetric-Website/>

Reference: Ahmad I, Chowdhury FS, Boullerne AI, Gow A, Feinstein DL. MyeliMetric: A Python-Based Toolbox for Standardized G-Ratio Analysis of Axon-Myelin Integrity. ASN Neuro. 2025;18(1):2603411.

Biological Validation of Machine-Learning-Defined Recovery States in the Locus Coeruleus-Noradrenergic-Glial Axis During Cuprizone Demyelination and Remyelination

Intakhar Ahmad¹, Zachary McDonald¹, Douglas L. Feinstein^{1,2}

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The locus coeruleus (LC) supplies major noradrenergic input to the brain, where noradrenaline (NA) regulates glial inflammation, trophic support, and cAMP-dependent signaling. We examined if a machine-learning transcriptomic state could quantify recovery from cuprizone (CPZ)-induced demyelination, supported by independent changes in the LC-NA system, glial composition, oligodendrocyte/myelin gene expression, and cAMP signaling. In this study, female C57BL/6 mice received 0.2% CPZ for 5 weeks, then 2 weeks on control chow (rCTL) or chow with 100 ppm lanthionine ketimine ethyl ester (rLKE). The study included CTL, CPZ, rCTL, and rLKE groups (n=4 each). LC integrity was assessed by tyrosine hydroxylase (TH) immunoreactivity; NA levels were measured in LC target regions; and corpus-callosum RNA-seq was integrated with machine learning, a myelin-associated expression score, and cell-type deconvolution. Cellular experiments tested LKE effects on cAMP and Ca²⁺ signaling. CPZ resulted in 219 differentially expressed genes, reduced LC TH immunoreactivity, and lower NA in target regions. Hippocampal NA was significantly reduced (p=0.0238), with a near-significant decrease in the corpus callosum (p=0.0525). These results identify LC-noradrenergic dysfunction as a feature of CPZ demyelination. RNA-seq data built a machine-learning model using CTL and CPZ animals, with the top 500 variable genes, PCA explaining 85.3% of variance, and a regularized logistic regression. The recovery index showed recovery groups moving away from CPZ toward CTL (p=0.086). The model served as an exploratory recovery measure, not a treatment classifier.

A biologically constrained myelin-associated expression score independently quantified recovery of oligodendrocyte/myelin transcription:

$$MES_i = [z(\text{Mbp}_i) + z(\text{Plp1}_i) + z(\text{Mog}_i) + z(\text{Ernn}_i) + z(\text{Myrf}_i)] / 5$$

where $z(\text{gene}_i) = [\text{expression}(\text{gene}_i) - \text{mean expression}(\text{gene})] / \text{SD}(\text{gene})$ for animal i. MES increased from -1.17 ± 0.64 in CPZ animals to 0.53 ± 0.08 in rLKE (p=0.029; Cohen's d=1.86). The rLKE-rCTL difference almost reached significance (p=0.057).

The 5-week RNA-seq experiment was independently analyzed using marker-based NNLS deconvolution, estimating contributions from various cell types. CPZ increased DAM-like microglia and decreased oligodendrocytes. During recovery, DAM-like microglia declined, and oligodendrocyte estimates shifted toward controls. rLKE showed a lower DAM-like estimate than rCTL, but oligodendrocyte recovery was evident in both. Thus, an independent cellular composition estimate confirmed the injury-to-recovery trend identified by the multigene machine-learning model.

Transcriptomic and cellular signaling results linked the LC-NA/cAMP axis. Recovery-related RNA-seq changes involved components of adrenergic and adenylate cyclase pathways, such as *Adrb1*, *Adcy1*, and *Adcy9*. LKE significantly increased cAMP after 60 minutes in primary mouse astrocytes, microglia, rat C6 cells, and mouse OliNeu cells. Adenylate cyclase inhibitors reduced the LKE-induced cAMP response depending on cell type: ST034307 decreased cAMP in C6 and OliNeu cells, while DIA reduced cAMP in all tested cells except microglia. LKE also increased Ca²⁺ in C6 cells by about two-fold, supporting a link between LKE, Ca²⁺-sensitive adenylate cyclase, and cAMP production.

The trophic arm of this pathway showed a parallel biological pattern. BDNF, a cAMP-responsive neurotrophin that provides retrograde support to LC neurons, showed reduced staining after 5-week CPZ exposure, increased staining during spontaneous recovery, and a stronger BDNF signal during LKE-associated recovery, with BDNF immunoreactivity co-localizing with GFAP in immunohistochemistry. These findings align with the transcriptomic movement toward a recovery state and with restoration of myelin-associated gene expression.

These data support a model where 5-week CPZ demyelination involves LC dysfunction, reduced NA, expansion of DAM-like microglia, and loss of oligodendrocyte signals. A machine-learning model trained on CTL and CPZ animals identified recovery animals reverting toward control transcriptomic states. MES and NNLS deconvolution validated this trajectory. Recovery with LKE involved changes in *Adrb1*, *Adcy1*, and *Adcy9*, increased Ca²⁺-linked cAMP in glia, enhanced BDNF signaling, decreased DAM-like microglia, and restored myelin gene expression. These findings support an LC-NA/cAMP framework for demyelination and recovery, with future validation needed for downstream PKA/CREB activation and pathway dependence.

Liver Kinase B1 Deficiency Alters Pantothenic Acid Metabolism and Iron Accumulation, and Increases Ferroptosis in Astrocytes

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Astrocytes maintain metabolic homeostasis and iron balance in the CNS, and iron accumulation is a hallmark of chronic multiple sclerosis (MS) lesions. Loss of liver kinase B1 (LKB1) disrupts metabolic pathways and mitochondrial function, both essential for cellular resilience. This study investigated whether LKB1 deficiency impairs iron handling and pantothenate (PA) metabolism, raising ferroptosis susceptibility, with relevance to MS and conceptual overlap with Neurodegeneration with Brain Iron Accumulation (NBIA). Primary mouse astrocytes were treated with siRNA to knockdown (KD) LKB1 expression and were compared to wild-type (WT) controls. Metabolomics and qPCR characterized the PA : Coenzyme A (CoA) pathway as being enriched in the KD cells. Cells were examined under basal conditions and following exposure to the ferroptosis inducer Erastin. Viability was quantified by LDH release, and intracellular iron by Perl's staining. Iron-regulatory proteins (transferrin, transferrin receptor, ferritin, DMT1) were analyzed. Conditioned media (CM) from WT or KD astrocytes were applied to evaluate protective effects. KD astrocytes displayed disrupted PA : CoA metabolism and heightened sensitivity to Erastin. Iron accumulation was markedly increased (~38–40% vs. ~2% in WT; $p < 0.05$), accompanied by reduced transferrin receptor expression and a modest rise in ferritin. CM from WT cells partially rescued KD viability, while CM from KD cells provided greater protection, suggesting that secreted factors such as lipocalin 2 (LCN2) may chelate iron and confer resistance to ferroptosis. These findings indicate that LKB1 is essential for sustaining iron regulation and PA-dependent metabolic pathways that shield astrocytes from ferroptosis. Disruption of these mechanisms may connect astrocytic metabolic dysfunction to neurodegeneration in MS, mirroring features observed in NBIA. Astrocyte-derived factors like LCN2 may represent an endogenous protective mechanism and a potential therapeutic target.

This work was supported by the National Multiple Sclerosis Society and the Department of Veterans Affairs.

XBP1s Activation in Oligodendrocyte Progenitor Cells as a Potential Therapeutic Strategy for Remyelination in Multiple Sclerosis

K. Bruce, **L. Allende**, G. Newell, J. Chan-Zervas, A. Chapagai, Y. Chen

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Background: Multiple Sclerosis (MS) is a chronic autoimmune disease characterized by inflammatory demyelination and oligodendrocyte loss in the central nervous system (CNS). Oligodendrocyte progenitor cells (OPCs) must differentiate into mature oligodendrocytes to restore myelin; however, inflammation and endoplasmic reticulum (ER) stress impair this process. The unfolded protein response (UPR) is an adaptive ER stress pathway, and one of its key branches involves inositol-requiring enzyme 1 (IRE1), which splices X-box binding protein 1 (XBP1) mRNA to generate the active transcription factor XBP1s. Although XBP1s has been implicated in Schwann cell-mediated remyelination after peripheral nerve injury, its role in OPCs during CNS remyelination under inflammatory conditions remains unclear.

Objective: To determine whether targeted overexpression of XBP1s in OPCs promotes OPC differentiation, oligodendrocyte maturation, and remyelination in an inflammatory mouse model of MS.

Methods: Rosa26^{fl-stop-fl-XBP1s} mice were crossed with PDGFRa-CreER^{T2} mice to generate Rosa26^{fl-stop-fl-XBP1s};PDGFRa-CreER^{T2} animals, allowing tamoxifen-inducible XBP1s overexpression in OPCs. Control mice lacked Cre expression. Both groups received tamoxifen for 5 days followed by a 10-day washout. Mice were then subjected to a combined inflammatory demyelination/remyelination model: 3 weeks of cuprizone diet, 1 week of normal chow, and 2 weeks of Experimental Autoimmune Encephalomyelitis (EAE) induced with MOG₃₅₋₅₅ plus Pertussis Toxin. Tissues were collected at 0 weeks (0W), 3 weeks (3W), and 6 weeks (6W). The corpus callosum was analyzed by electron microscopy (EM) and immunofluorescence.

Results: Both Rosa26^{XBP1s};PDGFRa-Cre group and control group showed increased T-cell numbers in the corpus callosum at 6W relative to 0W and 3W. At 3W, Rosa26^{XBP1s};PDGFRa-Cre mice showed a decline in proliferating OPCs and reduced OPC density. By 6W, however, OPCs recruitment and density were comparable between groups. Notably, mature oligodendrocyte numbers were increased in Rosa26^{XBP1s};PDGFRa-Cre mice at both 3W and 6W compared with controls, suggesting that overexpressed Xbp1s may promote the differentiation of OPCs. EM analysis at 6W revealed a significant increase in myelinated axons and a higher G-ratio in Rosa26^{XBP1s};PDGFRa-Cre mice, indicating enhanced remyelination during inflammation. To complement these findings, ongoing in vitro studies using tamoxifen-treated primary OPCs are evaluating whether XBP1s overexpression protects against interferon-gamma-induced stress.

Conclusions: Overexpression of XBP1s in OPCs increases mature oligodendrocyte numbers and improves remyelination under inflammatory conditions. These findings suggest that targeted activation of the IRE1/XBP1s branch of the UPR may represent a promising therapeutic avenue for promoting myelin repair in MS.

Investigating the Impact of XBP1s Transgenic Overexpression in Mature Oligodendrocytes in a Multiple Sclerosis Mouse Model

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Multiple Sclerosis (MS) is an autoimmune disorder best characterized by immune cell-mediated demyelination within the central nervous system (CNS). Mature oligodendrocytes are the sole producers of myelin within the CNS and therefore represent an important cellular target for the development of regenerative treatments for MS. During MS, the remyelination process, in combination with the inflammatory environment, imposes a tremendous load on the oligodendrocyte secretory pathway, for which the endoplasmic reticulum (ER) serves as a central organelle. Consequently, unfolded proteins can accumulate within the ER, initiating the unfolded protein response (UPR). The UPR is an adaptive cellular homeostatic response that attempts to restore ER proteostasis through three distinct pathways: activating transcription factor 6 (ATF6), inositol-requiring enzyme 1 (IRE1), and protein kinase R-like endoplasmic reticulum kinase (PERK). While the roles of the ATF6 and PERK pathways have been interrogated within the oligodendrocyte niche, the contribution of IRE1 activation and its downstream signaling targets to oligodendrocyte maturation, survival and myelination during MS remains poorly understood.

Here, using PLP-Cre;Rosa26-XBP1s mice, we demonstrate that transgenic overexpression of X-box binding protein 1 spliced (XBP1s), the transcription factor activated at the downstream of IRE1, within mature oligodendrocytes, ameliorates clinical symptoms in experimental autoimmune encephalomyelitis (EAE), a murine model of MS. Immunohistochemistry analysis confirmed a marked decrease in lesion size and significant increases in the number mature oligodendrocytes within the lumbar spinal cord (LSC). Additionally, XBP1s overexpression in oligodendrocytes significantly decreased caspase 3+ apoptotic oligodendrocytes in LSC. Interestingly, we also observed reduced infiltration of CD3+ T cells within the LSC. Finally, electron microscopy analysis revealed a significant increase in the number of myelinated axons within the LSC region of PLP-Cre;Rosa26-XBP1s mice. Overall, our data indicates that IRE1/XBP1s activation within mature oligodendrocytes may represent a promising therapeutic strategy to enhance oligodendrocyte survival and myelination while simultaneously reducing CNS immune cell infiltration.

cGAS–STING Signaling in Alzheimer’s Disease and Amyotrophic Lateral Sclerosis: Distinct Cellular Triggers Converge on Neuroinflammation

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4. University of Nevada Reno School of Medicine, Reno, Nevada, USA
5. Department of Neurology, Carson Tahoe Health, Carson City, Nevada, USA

Neuroinflammation contributes to Alzheimer’s disease (AD) and amyotrophic lateral sclerosis (ALS), but whether these disorders converge on a shared innate-immune stress pathway remains unclear. Cyclic GMP–AMP synthase (cGAS) senses cytosolic DNA and signals through stimulator of interferon genes (STING) to activate TBK1/IRF3 and NF-κB, linking cellular injury to type I interferon and inflammatory responses. We performed a focused literature synthesis of mechanistic studies evaluating cGAS–STING signaling in AD and ALS, emphasizing upstream triggers, cellular context, glial responses, and pathway-directed interventions.

In AD, evidence is strongest in microglia. Pathogenic tau activates microglial cGAS through mitochondrial DNA (mtDNA) leakage and through a PQBP1-dependent mechanism, while AD-linked APOE4 and TREM2 R47H amplify cGAS-associated interferon signaling and senescence-like microglial states. In 5xFAD models, genetic loss of cGAS or STING reduces type I interferon signaling, alters microglial activation, decreases amyloid-associated pathology and neuritic injury, and preserves cognition. Microglial cGAS deficiency also limits

disease-associated reactive astrocyte responses. Notably, pathway suppression reduces inflammatory signaling while improving amyloid control, suggesting that detrimental innate-immune activation may be separable from beneficial microglial functions.

In ALS, a distinct upstream route converges on the same axis. Cytoplasmic TDP-43 enters mitochondria, promotes mtDNA release through the mitochondrial permeability transition pore, and activates cGAS–STING signaling, with elevated cGAMP detected in ALS spinal cord. C9orf72 deficiency further amplifies STING-dependent type I interferon signaling by impairing autolysosomal STING degradation. Consistent with this mechanism, human C9-ALS tissue demonstrates prominent interferon-stimulated gene signatures, supporting genotype-dependent amplification of innate immune signaling. Emerging evidence also implicates microglial cGAS activation downstream of neuronal TDP-43 pathology. Across experimental models, genetic or pharmacologic pathway suppression reduces inflammatory signaling and neurodegenerative phenotypes, although much of the mechanistic ALS evidence remains derived from experimental TDP-43 and genetic models.

Together, these findings support cGAS–STING as a convergent stress-to-inflammation axis in AD and ALS but reveal distinct cellular origins and disease-specific modifiers. Predominantly microglial sensing of amyloid- and tau-associated stress characterizes AD, whereas ALS involves mtDNA release downstream of proteinopathy with both neuronal and myeloid contributions. These differences suggest that therapeutic targeting of cGAS–STING may require disease-, cell-, and context-specific approaches rather than uniform pathway suppression.

Optimizing lipid-siRNA conjugates for microglial gene silencing in Alzheimer's disease

Authors: Emma L. Fritsch¹, Alexander Sorets², Nora Francini³, Gowtham Raj³, Adam Abdulrahman³, Alexander Ligocki², Joshua Park², Craig Duvall², Ethan Lippmann^{1,2,3}

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Microglia are increasingly recognized as key drivers of neurodegenerative disease, and genetic studies have linked numerous microglial genes to late-onset Alzheimer's disease (AD). Among these, *CD33* encodes an inhibitory sialic-acid-binding receptor associated with altered amyloid-beta plaque burden and cognitive decline in AD. In humans, alternative splicing generates two functionally distinct CD33 isoforms with opposing associations with AD risk: the full-length isoform, CD33M, is associated with increased AD risk, whereas the shorter isoform, CD33m, is associated with reduced AD risk. Thus, selectively silencing CD33M while preserving CD33m constitutes an underexplored therapeutic opportunity for AD.

Microglia are challenging therapeutic targets because their phagocytic and degradative functions can limit cytosolic delivery of nucleic acid therapeutics. Although small interfering RNA (siRNA) could enable selective CD33M silencing, unmodified siRNAs inefficiently transfect microglia. Our laboratory previously developed a lipid-siRNA conjugate, termed L2-Gen1, that achieved 25% huntingtin (*Htt*) gene silencing in microglia one month after intracerebroventricular (ICV) administration. To improve myeloid-cell delivery, we optimized the lipid conjugate to generate L2-Gen2 and compare its *in vivo* activity with that of L2-Gen1 following ICV administration in mice. Using *Htt* as a proof-of concept target, we measured mRNA expression in CD11b-positive cells two and six weeks after treatment. We next investigated *in vivo* silencing of mouse *Cd33* using the L2-Gen2 platform. Finally, we began developing isoform-specific human *CD33* siRNAs.

L2-Gen2 produced greater *Htt* mRNA reduction in CD11b-positive cells at two weeks (60%) than L2-Gen1 did at one month (25%). *Htt* silencing by L2-Gen2 in CD11b-positive cells increased to 75% at six weeks, demonstrating sustained and progressively enhanced microglial knockdown. We next designed siRNAs targeting *Cd33* and screened candidates *in vitro* using J774A.1 macrophages. The two most effective candidates, sequences 485 and 1500, achieved 70% and 55% *Cd33* silencing, respectively. Following ICV administration of these siRNAs using L2-Gen2, sequence 485 achieved 40% *Cd33* knockdown in CD11b-positive cells at two weeks without overt toxicity. Finally, preliminary screening of human *CD33* siRNAs identified two effective candidates targeting total *CD33*. Ongoing screening seeks to identify a *CD33M*-selective siRNA capable of isoform-specific knockdown.

Together, these findings establish L2-Gen2 as an effective lipid-siRNA conjugate for myeloid cell gene silencing *in vivo*, producing sustained and progressively enhanced knockdown for at least six weeks after ICV administration. L2-Gen2 also enabled promising *in vivo* silencing of mouse *Cd33* at two weeks and provides a foundation for developing isoform-selective *CD33* siRNAs to use in humanized *CD33* mouse models. These findings support further investigation of microglial *CD33M* silencing as a potential therapeutic strategy for AD.

Pharmacological Enhancement of IRE1 Signaling Confers Protection in Multiple Sclerosis Mouse Model

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Multiple Sclerosis (MS) is an autoimmune disorder characterized with oligodendrocyte death and demyelination, which leads to axonal degeneration within the Central Nervous System (CNS). Current research suggests that the CNS inflammation triggers endoplasmic reticular (ER) and oxidative stress which promotes tissue damage. ER stress triggers the cellular adaptive mechanism of the unfolded protein response (UPR). Orchestrated through 3 transmembrane signals pathways (IRE1, PERK, and ATF6), the UPR works to provide a cytoprotecting role by maintaining cellular protein homeostasis. Our lab and others have shown that activation of the either the PERK or ATF6 pathways provides protection for oligodendrocytes and attenuates disease progression of a MS mouse model, Experimental Autoimmune Encephalomyelitis (EAE). However, the role of the IRE1 branch of the UPR in CNS protection within the inflammatory demyelination remains unclear. Upon stress, IRE1 cuts un-spliced Xbp1 mRNA and generates the active transcription factor Xbp1s to enhance ER protein folding capacity and quality control, thereby promoting cellular survival. Preliminary data in our lab suggests that genetic overexpression of XBP1s in oligodendrocytes reduces EAE disease severity and promotes oligodendrocyte survival. IXA4 is a selective activator of the IRE1/XBP1s pathway that enhances IRE1 RNase-mediated XBP1 mRNA splicing. Here we investigate the therapeutic effects of IXA4 on an EAE model and determine whether pharmacological activation of the IRE1/XBP1s pathway promotes oligodendrocyte survival and protects against CNS inflammation and demyelination. In this study, we induced EAE in 10-week-old female C57BL/6 mice, which we treated using daily i.p injections of IXA4 starting from post immunization day 2 and evaluated the severity of disease by scoring clinical symptoms. We showed that treatment with IXA4 treatment increased *Xbp1s* expression in the spinal cord of EAE mice through RT-qPCR analysis. Clinical assessment showed that IXA4 treatment delayed the onset of clinical EAE relative to vehicle-treated mice and produced a modest reduction in peak clinical score. Using immunofluorescent staining, we found that increased Ki67⁺PDGFR α ⁺ OPCs, reduced H2AX⁺ oligodendrocytes, and fewer iNOS⁺ microglia, suggesting that IXA4 enhances OPC proliferation, protects oligodendrocytes from DNA damage, and reduces CNS inflammation. Additionally, flow cytometry analysis of the spinal cord and lymph nodes at day 12 post-immunization showed that IXA4-treated had reduced CD90.2⁺ T cells and CD4⁺ T cells in the spinal cord, suggesting the reduced CNS inflammatory infiltration. Interestingly, both live CD45 cells and CD90.2⁺ T cells are also decreased in both cervical and inguinal lymph nodes, suggesting IXA4 may act during the priming or clonal expansion phase of the autoreactive response. Overall, our findings indicate that pharmacological activation of the IRE1/XBP1s pathway with IXA4 confers neuroprotection and immunomodulatory effects, suggesting that the targeted activation of IRE1 branch of the UPR could be a promising therapeutic target for MS.

CNS and PNS Myelin g Ratios Under Normal Physiologic Conditions: Reworking the Original Donaldson & Hoke (1905) Data.

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In contemporary myelin biology, there is a growing trend to prioritize faster, more convenient methodologies for evaluating white matter structure over the quality of analysis. This shift may be accompanied by less attention to the mechanistic foundations of the methods in preclinical and clinical research. To address such trends, the current study assesses three approaches for estimating the myelin g ratio from electron microscopy data, which is the gold standard approach to measure the impacts of neuropathology and treatment strategies on white matter integrity. Of the models examined, two are consistent with and equivalent to the linear relation defined by the axon versus fiber diameter plot (the principal data). The final model is the canonical almost universally accepted method for measuring g ratio, vis. axon diameter / fiber diameter. This model is demonstrated to be internally inconsistent and discordant with the principal data and can lead to inaccurate conclusions about myelin integrity.

Increasing interest in non-invasive neuroimaging to measure g ratios clinically in physiologic and pathophysiologic studies, necessitates calibration with electron microscopy-derived g ratios. To this end, the models that have been developed for each methodologies are concordant; thus, MRI holds significant promise for accurate determination of myelin integrity in patients. On the other hand, it is currently unclear if the metrics measurable by this voxel-based technology may preclude application to gray matter myelin, and may limit its use to specific white matter tracts in which the fibers are unidirectional.

AMPLIFIED NEUROINFLAMMATORY RESPONSES TO CO-OCCURRING ALPHA-SYNUCLEIN AND AMYLOID PLAQUE PATHOLOGIES IN A RAT MODEL OF DEMENTIA WITH LEWY BODIES

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Goal: Neurodegenerative diseases have historically been associated with distinct proteinopathies, including amyloid-beta (A β) plaques and hyperphosphorylated tau tangles in Alzheimer's disease (AD) and phosphorylated α -synuclein (pSyn) Lewy bodies (LBs) in Parkinson's disease (PD). However, increasing evidence demonstrates that these AD and PD proteinopathies often co-occur with each other in neurodegenerative diseases, including Dementia with Lewy Bodies (DLB), characterized by the presence of LBs but also featuring A β plaque pathology, and occasionally, tau tangles. Individual A β and pSyn pathologies induce specific pro-inflammatory responses; however, whether their co-occurrence produces a distinct and more aggressive neuroinflammatory profile remains poorly understood.

Methods: We modeled DLB co-pathology by injecting α -syn preformed fibrils (PFFs) into TgF344-19 AD rats, which develop A β plaques and display cortical and hippocampal degeneration. PFF injections induce widespread pSyn pathology and nigrostriatal degeneration. Male and female TgF344-19 and wild-type (WT) rats received bilateral PFF or monomer injections and were euthanized 2 or 4 months after surgery. Quantification of pSyn and A β pathology load, and immunoreactive area of microglia (Iba1) and astrocytes (GFAP) in the cingulate cortex (CC), basolateral amygdala (BLA), and entorhinal cortex (EC), was conducted using immunohistochemistry. Bulk RNA Sequencing was conducted on microdissected BLA and EC.

Results: PFF-injected TgF344-19 rats developed robust A β -pSyn co-pathology in the CC, BLA, and EC. In the EC, the presence of A β was associated with significantly greater pSyn burden ($p < 0.0001$). In the EC, microglial and astrocytic load was greatest in the presence of both pathologies, suggesting enhanced neuroinflammation. Bulk RNA-Seq results revealed that co-occurrence of pSyn and A β pathologies result in upregulation of hundreds of transcripts associated with numerous immune response programs, the majority of which were not associated with pSyn or A β pathology alone.

Conclusion: Our results suggest that A β and pSyn co-pathology potentiates immune response in DLB-relevant regions compared to either pathology alone.

Microglial, neuroinflammatory, and cognitive responses to high-fat diet-feeding in genetically diverse mice

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Obesity, prediabetes, and diabetes – which are growing in prevalence – put patients at increased risk for cognitive impairment (CI), including dementias such as Alzheimer’s disease. On-going research leveraging inbred mouse models of diet-induced obesity has indicated that neuroinflammatory mechanisms – including those mediated by microglia, the resident immune cells of the brain – are a potential underlying mechanism driving metabolic stress-induced CI. However, the use of genetically-diverse outbred mice – namely the Diversity Outbred (DO) mice – may represent a novel, more translatable model to study the impact of variable genetic predisposition and disease susceptibility, highlighting population-level disease dynamics which better mirror the response in humans. Thus, to investigate metabolic stress-induced CI in a model that more closely mimics the genetic diversity of the human population, we performed a pilot study investigating the metabolic, cognitive, and inflammatory effects of 14-17 weeks of high-fat diet (HFD)-feeding in female DO mice. HFD caused an expected increase in body weight and fasting plasma insulin as well as a decrease in glucose tolerance. Traditional cognitive assessments (puzzle box, Morris Water Maze, and fear conditioning) indicated similar executive functioning and learning and memory responses between control and HFD mice. However, home cage monitoring revealed an increase in anxiety-like behaviors including increased time near walls, more sleep bouts, and decreased sociability due to HFD feeding. In line with results from traditional cognitive assessments, HFD did not increase whole brain or microglial-specific inflammatory cytokines or upstream effector expression. Collectively, these results suggest that female DO mice exhibit a trend towards anxiety-like behaviors in response to chronic HFD, though increased time on diet may be necessary to appropriately model metabolic stress-induced neuroinflammation and CI.

T₁ Relaxation Times in the Human Corpus Callosum Reflect the Density of Myelinated and Unmyelinated Axons

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Introduction

The corpus callosum (CC), the largest cerebral commissure, is microstructurally heterogenous along its anterior-posterior extent. The genu contains densely packed, small-diameter axons, many of which are unmyelinated, the body is dominated by sparsely packed large-diameter myelinated fibers, and the splenium presents a mixture of the two types of axons (Aboitiz et al., Brain Res, 1992). Using a refined midsagittal CC parcellation scheme, Björnholm et al. (2017) demonstrated that T₁ across the CC follows this histological gradient, from the lowest in the genu, to the highest in the body, thus corresponding to the distribution of small-diameter axons (Aboitiz et al., 1992). This pattern is consistent with evidence that T₁ relaxation in white matter is dominated by magnetization transfer (MT) effects, whereby the apparent attenuation in T₁ relaxation times is driven by the number of protons at the fiber surface (axon microstructure) exchanging with protons from mobile water. Therefore, T₁ likely scales with the density of myelinated and unmyelinated axons rather than myelin content. Moreover, using a coarse CC parcellation scheme, Kauppinen et al. (2023) reported a similar anterior-posterior gradient; however, they attributed T₁ variation in lateral extensions of CC subregions to fiber orientation effects, a mechanism requiring no attribution to macromolecular content. We therefore sought to replicate that CC T₁ profile using an optimized MP2RAGE protocol, and to test the orientation hypothesis by extending the parcellation to medial and lateral divisions.

Methods

Forty-nine young adults (18M and 31F, mean age±SD 25.2±3.0 years) underwent an optimized MP2RAGE protocol designed to maximize UNI-signal linearity with T₁ across the physiological range of interest, thereby improving T₁ accuracy over traditional MP2RAGE protocols. The acquisition parameters were: TR=4,500ms, TI_{1,2}=400ms and 2,350ms, FA_{1,2}=6° both, BW= 369Hz, voxel=1×1×1mm³, TA=7:36 min). The CC was parcellated into 10 ROIs along the anterior-posterior axis, each split into medial and lateral (left and right) divisions (Lynn et al., 2021), and mean T₁ extracted from each. Two GEE models were ran to assess ROI and ROI × Side effects.

Results

A significant region effect was found in medial segments: $\chi^2(9) = 45.41$, $p < .0001$, with T₁ lowest in the genu, highest in the body, and intermediate in the isthmus/splenium. No overall left-right differences were found ($p = .37$). A significant ROI × Side interaction was found ($\chi^2(18) = 42.16$, $p < .0001$). Lateral T₁ values were lower than medial T₁ in most regions ($p < .0001$) except the genu (GENU-2) and the splenium subdivisions.

Conclusions

Using an independent acquisition and estimation approach, we replicated the anterior-posterior T₁ profile (Björnholm et al., 2017). This generalized CC T₁ gradient is likely to reflect (via MT effects) biological properties of the regions like the fiber density of the axon microstructure. The CC profile of inferred myelin content from Lynn et al. (2021) differs from the T₁ profile observed here, which contradicts the traditional view of T₁ as a marker of myelin content. Lastly, the medial-lateral pattern observed here was opposite in direction to that predicted by fiber orientation and is notably absent in the splenium, which is inconsistent with orientation as the dominant driver of regional T₁ variation in the CC.

Lanthionine Ketenimine Ethyl Ester Stimulates cAMP Production and Increases in Cytosolic Calcium in Glial Cells

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Multiple sclerosis (MS) is a chronic autoimmune disorder characterized by demyelination and neurodegeneration in the CNS, leading to significant disability. Previous studies have shown that Lanthionine Ketenimine Ethyl Ester (LKE) significantly reduces disease in various neurodegenerative disease models such as AD and PD. In our studies we've shown that LKE reduces disease severity in the Experimental Autoimmune Encephalomyelitis mouse model of MS; accelerates remyelination following cuprizone-induced demyelination; reduces microglial cell activation and increases oligodendrocyte progenitor cell (OPC) maturation both in vitro and in vivo. However, the precise mechanisms by which LKE mediates these effects are not established. Since OPC maturation and glial cell activation are regulated by the prototypical second messenger cAMP, we tested the possibility that LKE acts, at least in part, by regulating cAMP levels. In both primary mouse astrocytes and microglia LKE caused dose-dependent stimulation of cAMP production; with similar results observed in the C6 glioma and Oli-neu OPC cell lines; and with similar EC50 concentrations for astrocytes, microglia, and Oli-neu (2.4, 1.8, and 3.3 μ M, respectively). cAMP is known to increase phospho-CREB (p-CREB) expression by binding to and activating Protein Kinase A, which then phosphorylates CREB. Immunocytochemistry revealed an increase in phospho-CREB (p-CREB) expression in primary astrocytes after LKE treatment, providing further evidence that LKE may regulate levels of cAMP. Initial findings suggest that effects of LKE on primary mouse OPCs are less robust than observed in the Oli-neu cells. We previously showed that LKE interacts with the axonal modulator collapsin response mediator protein 2 (CRMP2) and modulates calcium influx in primary OPCs. We therefore tested if LKE effects on cAMP were mediated by activation of calcium-dependent adenylate cyclases (AC) AC1 and AC8. In initial studies we found that the LKE-induced cAMP increases in astrocytes were reduced in the presence of the broad AC inhibitor 2',5'-dideoxyadenosine (2',5'-ddA) as well as the selective AC1 inhibitor ST034307 (ST34). Interestingly, cAMP increases due to the AC activator forskolin (FSK) were also blocked by these inhibitors. These findings suggest that LKE-dependent increases in cytosolic calcium contribute to activation of AC1 and/or AC8. Subsequent experiments utilizing the Fluor-4 NW calcium indicator, have shown that LKE increases cytosolic calcium in C6 cells, and that treatment with chelated calcium free media (EGTA 2 mM) did not affect these cytosolic increases. This suggests that cytosolic calcium increases may be due to intracellular sources—most likely the endoplasmic reticulum. Ongoing studies are designed to confirm an association between increased intracellular calcium concentrations and cAMP production, and to use qPCR to determine the cell-specific expression of calcium-dependent and independent AC isoforms. Overall, our results provide the first demonstration that LKE modulates cAMP production, and, that cytosolic calcium may be from intracellular stores, providing a new avenue for understanding the therapeutic actions of LKE in MS and other diseases.

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Therapeutic Modulation of the Integrated Stress Response Preserves Visual Circuit Function and Alters Microglia Reactivity during Inflammatory Demyelination

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Multiple sclerosis (MS) is an inflammatory demyelinating disease that leads to progressive neurological decline despite available disease-modifying therapies. Elucidating mechanisms of neurodegeneration is therefore critical for developing neuroprotective strategies. The visual system is highly relevant in this context because it is among the most frequently affected neural circuits in people with MS. Our lab recently showed that reactive microglia eliminate retinal ganglion cell presynaptic terminals in the visual thalamus during MS-relevant disease models, contributing to visual circuit dysfunction, but the upstream pathways regulating neuronal vulnerability and microglial reactivity remain poorly understood. The integrated stress response (ISR) is a stress-adaptive pathway whose components are upregulated in MS lesions. Although the ISR can be cytoprotective when acutely engaged, sustained ISR activation can promote neuronal dysfunction and alter microglial inflammatory states, making it a promising therapeutic target. In MS-relevant animal models, genetic ISR inhibition has been shown to protect visual function. However, whether ISR manipulation affects synaptic pathology or if the benefits for visual function can be achieved after the onset of clinical symptoms remains unclear. We investigated whether post-onset pharmacologic attenuation of ISR output protects visual circuits in experimental autoimmune encephalomyelitis (EAE), a widely used preclinical model of MS. We administered a small molecule inhibitor of ISR activation after the onset of EAE clinical symptoms, and visual function was tracked longitudinally using optomotor testing and pattern-stimulated visual evoked potential (VEP) recordings. Our data show that therapeutic attenuation of ISR output significantly improved both visual acuity and VEP responses during peak and chronic EAE, despite persistent immune cell infiltration. ISR modulation also preserved presynaptic terminals in the visual thalamus and increased microglial expression of homeostatic marker TMEM119 compared with vehicle-treated EAE mice. Our ongoing work is evaluating whether these effects are associated with altered microglial reactivity and microglia–synapse interactions, as well as changes in other hallmark MS pathologies including synaptic organization, gliosis, neuronal cell death, and demyelination. Together, these studies will define how therapeutic ISR modulation affects microglial state and visual circuit integrity and may identify new strategies for neuroprotection in MS.

Disease-Associated Microglia Promote Visual Circuit Dysfunction in Demyelinating Disease

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Microglia are the resident innate immune cells of the central nervous system and constantly surveil their microenvironment under homeostatic conditions. Our previous work showed that, across multiple preclinical models of multiple sclerosis (MS), an inflammatory demyelinating and neurodegenerative disease, microglia become reactive and eliminate retinal ganglion cell (RGC) synapses in the lateral geniculate nucleus (LGN). This synaptic loss occurs early and drives visual dysfunction, at least in part, independently of other hallmark MS pathologies. While several reactive microglial phenotypes exist, it remains unclear which reactive phenotype these synapse-engulfing microglia adopt and whether this transition is required for synaptic circuit disruption and visual decline.

Our new data show decreased synaptic densities selectively surrounding microglia that adopted the so-called disease-associated microglia phenotype (DAM) in the visual system, which comprises the predominant reactive microglial state described across neurodegenerative diseases. These data suggest a role for this microglial state in synaptic circuit disruption during demyelinating disease; thus, we tested whether blocking the DAM transition protects against synapse loss and visual dysfunction in demyelinating disease. To test this, we genetically deleted spleen tyrosine kinase (*Syk*) in microglia or pharmacologically inhibited SYK, a key regulator of microglial acquisition of the DAM phenotype. Using these complementary approaches, we determined whether blocking the homeostatic-to-DAM transition alters synaptic connectivity in experimental autoimmune encephalomyelitis (EAE), an MS-relevant mouse model. We found that microglia-specific *Syk* deletion or pharmacological SYK inhibition reduced the DAM transition, preserved synaptic circuitry, and improved visual function in EAE. These findings implicate acquisition of the DAM phenotype in microglia-mediated synapse loss and visual dysfunction in EAE and support modulation of the SYK–DAM pathway as a potential therapeutic strategy to protect visual circuit integrity in MS-relevant disease contexts and other neuroinflammatory eye diseases.

Title: Immunoproteasome Regulation of Neuron–Microglia Interactions During Visual Synapse Loss and Repair in Multiple Sclerosis

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Progressive neurodegeneration remains an important unsolved problem in multiple sclerosis (MS), as current therapies reduce inflammatory demyelinating activity but do not reliably halt or reverse ongoing neurodegeneration and disability. The visual circuit is of particular interest because visual dysfunction occurs early and frequently in MS. In multiple preclinical MS models, we have identified microglia-mediated loss of retinal ganglion cell (RGC) synaptic terminals in the lateral geniculate nucleus (LGN) that causes visual deficits and precedes detectable RGC axonal degeneration or cell death, highlighting the importance of neuron-microglia interactions in MS-associated visual circuit degeneration. In MS-relevant experimental autoimmune encephalomyelitis (EAE), early synaptic loss persists into later disease stages despite RGC survival, suggesting that endogenous repair is limited in this inflammatory demyelinating context.

To identify candidate mechanisms associated with persistent synaptic loss, we performed proteomic profiling of isolated synaptic terminals from the LGN during EAE. Analysis of the synaptic proteome revealed increased PSMB8, the catalytic $\beta 5i$ subunit of the immunoproteasome, and immunostaining confirmed persistent PSMB8 elevation in RGC presynaptic terminals throughout the EAE disease course. These findings suggest that immunoproteasome induction coincides with EAE-associated RGC synaptic disassembly and lack of spontaneous synaptic repair.

In contrast, in the cuprizone model of demyelination and remyelination, RGC synapses partially recovered following their initial loss. However, this repair was incomplete, reminiscent of limited remyelination in MS. Notably, PSMB8 levels were elevated in RGC presynaptic terminals during degeneration but decreased during synaptic recovery, suggesting that immunoproteasome activity may promote synaptic disassembly and/or constrain repair. Consistent with this possibility, treatment of EAE mice with a PSMB8-specific inhibitor reduced clinical scores and improved optomotor contrast sensitivity. Because microglia mediate RGC synapse elimination and robustly upregulate immunoproteasome components during neuroinflammation, ongoing studies are determining whether PSMB8 inhibition alters microglial reactivity and synapse engulfment while distinguishing neuronal from microglial contributions to treatment efficacy. This work will determine whether and how the immunoproteasome regulates visual circuit degeneration and repair through neuronal and microglial pathways in MS-relevant disease.

Pharmacological Enhancement of IRE1 Signaling Confers Protection in Multiple Sclerosis Mouse Model

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Multiple Sclerosis (MS) is an autoimmune disorder characterized by the death of oligodendrocytes, demyelination, and progressive axon degeneration within the Central Nervous System (CNS), particularly in women. Oligodendrocytes are glial cells in the CNS that produce myelin. Myelin is a lipid-rich insulating sheath that surrounds axons, allowing for the rapid, saltatory conduction of electrical signals. In MS, immune-mediated inflammation targets oligodendrocytes, which then leads to inflammation, demyelination, and axonal degradation. Currently, there are limited therapeutic interventions for individuals affected by MS, meaning that there are limited strategies that enhance oligodendrocyte resilience to protect CNS tissue from inflammatory injury.

Chronic inflammation in MS pathology creates a hostile cellular environment that disrupts protein folding within the endoplasmic reticulum (ER), inducing ER stress. In response to this, cells activate an adaptive signaling network known as the unfolded protein response (UPR), which functions to restore protein homeostasis. The UPR is mediated by three primary transmembrane signaling arms: inositol-requiring enzyme 1 (IRE1), protein kinase RNA-like ER kinase (PERK), and activating transcription factor 6 (ATF6). Upon ER stress, IRE1 splices X-box binding protein 1 (XBP1) mRNA, which produces the active transcription factor XBP1s. XBP1s thereby enhances ER folding capacity and cellular survival under stress conditions. Preliminary data from Dr. Chen's lab indicate that genetic overexpression of XBP1s in an MS mouse model, Experimental Autoimmune Encephalomyelitis (EAE), reduces disease severity and improves oligodendrocyte survival. This suggests that selective activation of the IRE1/XBP1s pathway may be therapeutically beneficial.

This study aims to investigate the therapeutic impact of IXA4, a highly selective small-molecule activator of the IRE1/XBP1 pathway, on the EAE model and determine whether its pharmacological activation promotes oligodendrocyte survival and protects against CNS inflammation and demyelination. EAE was induced in 10-week-old female C57BL/6 mice, followed by daily intraperitoneal injection of IXA4 beginning on post-immunization day 2. Disease severity was monitored using clinical EAE scoring. RT-qPCR analysis demonstrated increased Xbp1s expression in the spinal cords of IXA4-treated EAE mice, providing support for the pharmacological activation of the IRE1 pathway in vivo. IXA4 treatment produced a modest decrease in peak disease severity compared with vehicle-treated

Immunofluorescent staining revealed increased numbers of Ki67⁺PDGFR α ⁺ oligodendrocyte precursor cells (OPCs), reduced H2AX⁺ oligodendrocytes, and fewer iNOS⁺ microglia following IXA4 treatment, which is consistent with enhanced OPC proliferation, reduced oligodendrocyte DNA damage, and attenuation of CNS inflammation. Flow cytometric analysis of spinal cord and lymphoid tissues at day 12 post-immunization further demonstrated reduced CD90.2⁺ T cells and CD4⁺ T cells in the spinal cord of IXA4-treated mice, suggesting decreased inflammatory T-cell accumulation within the CNS. Interestingly, live CD45 cells and CD90.2⁺ T cells were also reduced in cervical and inguinal lymph nodes. This raises questions regarding whether IXA4 may also influence peripheral immune activation during clonal expansion of reactive T cells.

In conclusion, our findings indicate that pharmacological activation of the IRE1/XBP1s pathway with IXA4 confers neuroprotection and immunomodulatory effects, suggesting that the targeted activation of the IRE1 branch of the UPR could be a promising therapeutic target for MS.

Integrated Stress Response in Microglia: A Key Player in A Multiple Sclerosis Model.

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Specialized central nervous system (CNS)-resident macrophages known as microglia play a critical role in tissue homeostasis and inflammatory response. These cells are responsible for immune surveillance in CNS parenchyma and perivascular space, monitoring for pathological insult. Upon recognition of CNS injury, microglia shift from a homeostatic to a proinflammatory state. The Integrated Stress Response (ISR) is a signaling pathway that protects the cells against various stress conditions by phosphorylating the alpha subunit of the translation initiation factor eIF2. Systemic activation of the ISR contributes to neurodegeneration via promotion of proinflammatory cytokine and toxic lipid production. However, the cell-type specific role of ISR in progression of neuroinflammation remains unexplored. Our central hypothesis is that microglial ISR is a primary regulator of neuronal damage and peripheral immune cell recruitment during neuroinflammation. To test this hypothesis, we will use an autoimmune neuroinflammation model (EAE) in a transgenic mouse lacking p-eIF2a (A/A^{Mac}) or GCN2 (nutrient-sensing upstream ISR kinase) in microglia. Our preliminary data show that A/A^{Mac} mice have an increased disease phenotype when subjected to EAE model, accompanied by an enrichment of cytotoxic CD8 T cells as well as helper Th17 cells in the spleen. Additionally, we found the gene expression profile of the sorted microglia correlates to disease severity. Bulk RNA-sequencing of sorted microglia has revealed increased expression of genes *Spp1* and *Htr2b* in A/A^{Mac} group, concomitant with a downregulation of glutamine regulators encoded by the *Slc38a3* and *Slc1a3* genes. These preliminary findings suggest that ISR activation in microglia promotes T cell recruitment, and the loss of the ISR pathway in microglia induces disease severity. We will continue to interrogate the ISR pathway using disease model, microglial GCN2 KO model, immune cell profiling, and high-throughput strategies, and compare the findings with human multiple sclerosis (MS) samples. The results of this study will establish a foundational framework for identifying macrophage-based therapies and designing clinical trials.

INVESTIGATING THE PROTECTIVE ROLE OF CRYSTALLIN ALPHA B IN OLIGODENDROCYTES DURING INFLAMMATORY DEMYELINATION

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Multiple Sclerosis (MS) is a neurodegenerative disease that is characterized by immune-mediated central nervous system (CNS) demyelination and oligodendrocyte loss. Inflammatory stress associated with MS contributes to endoplasmic reticulum (ER) stress and oxidative stress in the CNS. Crystallin alpha B (CRYAB) is a heat shock protein that has been shown to be cytoprotective previously. CRYAB acts as a molecular chaperone that can bind to misfolded proteins to prevent continuous unfolding and ability to bind to procaspase-3 to prevent its activation to caspase-3. Interestingly, a previous study suggested that CRYAB expression is associated with increased severity of demyelination through pathogenic responses of astrocytes in a cuprizone demyelination model. CRYAB is an abundant protein in oligodendrocytes, however its role in oligodendrocytes remains poorly understood. In the CNS, cellular stress can trigger the release of extracellular chaperones, which may function as damage-associated molecular patterns (DAMPs) and influence other glial cells, including astrocytes. We hypothesize that CRYAB released from stressed oligodendrocytes may act as a DAMP that activates reactive astrocytes and impairs recovery of CNS demyelination.

In this study, we utilized a conditional knockout mouse line to delete CRYAB expression in oligodendrocytes (*Cryab^{fl/fl}; Plp-Cre*). *Cryab^{fl/fl}* littermates were used as control. These mice were subjected to a 0.2% cuprizone toxin-induced demyelination model to investigate CRYAB during oxidative stress. Open field and beam walking behavior tests were conducted to investigate motor deficits caused by demyelination. Interestingly, *Cryab^{fl/fl}; Plp-Cre* mice exhibited better locomotor function, coordination and balance compared to *Cryab^{fl/fl}* control mice during week 3 and week 5 of cuprizone exposure. To further investigate the cellular response, brain tissue was collected to evaluate the corpus callosum using immunohistochemistry (IHC) to assess oligodendrocyte lineage cells, myelination, and other glial cells, including astrocytes. Preliminary analysis of oligodendrocyte lineage cells and caspase-3 staining were performed to assess oligodendrocyte loss, which showed no difference between *Cryab^{fl/fl}; Plp-Cre* and *Cryab^{fl/fl}* mice. Using markers of astrocyte reactivity of glial fibrillary acidic protein (GFAP) and S100A10, we revealed an increased percentage of GFAP and S100A10 density in the *Cryab^{fl/fl}; Plp-Cre*, compared to the *Cryab^{fl/fl}* mice. These findings suggest that CRYAB normally restrains astrocyte reactivity, including the protective/repairative S100A10+ state, and that loss of CRYAB unmasks this response. To test this directly, we examined the effects of CRYAB on astrocyte reactivity *in vitro*. Primary mouse astrocyte culture was stressed with a cytokine cocktail and then exposure to either vehicle or recombinant CRYAB protein. Our immunocytochemistry result showed that CRYAB treatment significantly reduced the S100A intensity of reactive astrocytes, consistent with the *in vivo* findings. Ongoing studies are examining the effect of CRYAB on neurotoxic astrocyte markers, and electron microscopy is being used to assess myelination and axon integrity in these mice.

In conclusion, our results suggest that oligodendrocyte-derived CRYAB modulates astrocyte reactivity, highlighting a novel form of oligodendrocyte-astrocyte crosstalk. This study will provide critical insight into cell-specific responses in MS and may identify novel therapeutic targets for promoting CNS protection.

OLIGODENDROCYTE-SPECIFIC LOSS OF CRYAB AMELIORATES MOTOR DEFICITS IN MS MOUSE MODELS

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Multiple Sclerosis (MS) is a neurodegenerative disease associated with inflammation in the central nervous system (CNS), resulting in oligodendrocyte apoptosis and demyelination of axons. Crystallin alpha B (CRYAB) is a heat shock protein with cytoprotective and anti-apoptotic properties in the CNS. Previous studies have shown that the absence of CRYAB accelerates disease progression in animal models of MS. While CRYAB acts as a protective shield inside the brain, it is also highly upregulated and expressed in active MS lesions, particularly in oligodendrocytes. However, how oligodendrocyte-derived CRYAB affects oligodendrocyte dynamics and neuroinflammation remains poorly understood. We hypothesize that CRYAB in oligodendrocytes protects against inflammatory demyelination in MS. To test the hypothesis, we used a conditional knockout mouse line to delete CRYAB expression in oligodendrocytes (*Cryab^{fl/fl}; Plp-Cre*) and *Cryab^{fl/fl}* littermates as a control. We first induced experimental autoimmune encephalomyelitis (EAE) in these mice and scored clinical symptoms from post-immunization day 7 to 35 to evaluate disease progression. In a second model, animals were subjected to cuprizone-induced demyelination, and behavioral tests were performed to assess motor and functional deficits. Open field and walking beam tests were performed at weeks 0, 3, and 5 of cuprizone exposure to measure the locomotion, balance, and coordination of the mice. In the EAE mouse model, disease severity did not differ significantly between the knockout mouse line and the control group. Surprisingly, in the cuprizone model, the *Cryab^{fl/fl}; Plp-Cre* mice travelled farther distances at a faster velocity at both weeks 3 and 5, compared to the control mice in the open field test. In the beam-walking test, no significant difference in latency was found at week 3 between the two groups walking on either 24mm- and 12mm-wide beams. At week 5, however, the *Cryab^{fl/fl}; Plp-Cre* showed significantly reduced latency on both beams, compared to the *Cryab^{fl/fl}* control. Additionally, the *Cryab^{fl/fl}; Plp-Cre* mice exhibited fewer slips on the 12mm beam at week 3 and on the 23mm beam at week 5. These findings suggest that the absence of CRYAB in oligodendrocytes significantly improved locomotion, coordination, and balance of mice following cuprizone-induced demyelination. In conclusion, our study illustrates a context-dependent role for oligodendrocyte CRYAB and challenges the current view of CRYAB as protective in demyelinating diseases. Ongoing experiments focus on how CRYAB regulates oligodendrocyte dynamics and astrocyte response, providing insight into the underlying mechanism of MS and potentially identifying future therapies for CNS protection.

In utero rodenticide exposure induces neuropathology in pups

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Rodenticide exposure, particularly from long-acting anticoagulant rodenticides (LAARs) such as superwarfarins, remains a significant public health concern due to their extreme potency and long biological half-life. These compounds disrupt the vitamin K cycle, leading to severe and sometimes fatal hemorrhage. Brodifacoum (BDF), one of the most widely used superwarfarins, poses additional risks during pregnancy, including long-term neurodevelopmental damage and the potential for Fetal Warfarin Syndrome (FWS). This project aims to evaluate whether cholestyramine (CSA), a drug typically used to treat hypercholesterolemia, can be utilized as a therapeutic agent to bind and remove BDF effectively, thereby reducing neurological injury in developing offspring. Using rabbit models, pregnant rabbits were exposed to BDF at gestational day 23, pups weaned, and neuroinflammatory and cognitive outcomes were assessed in pups at 7 and 14 days post-birth. Preliminary analyses comparing control to BDF-exposed pups revealed increased neuroinflammation, disrupted myelination, and alterations in MBP, PLP, and Caspr staining. Control pups consistently displayed greater white and gray matter area in MBP staining, while BDF-exposed pups exhibited increased node of Ranvier spacing, suggesting impaired neuronal conduction. When the dams were administered CSA, markers of neuroinflammation in the p14 day old pups was reduced. Initial behavior assessment shows that the BDF exposed pups displayed increased anxiety compared to control pups. These findings support that prenatal BDF exposure induces measurable and early neurological injury, and suggests that interventions to reduce BDF levels could reduce subsequent consequences.

Neuronal Activity-Dependent Glia-Secreted Regulators of Synapses in Inflammatory Demyelinating Disease

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Multiple sclerosis (MS) is a neurodegenerative disease characterized by inflammatory demyelination, neurodegeneration, and progressive disability over time. While treatments managing inflammation and associated symptoms are available, addressing continuous neurodegeneration remains challenging. MS manifestations frequently impact the visual system, and previous results from our lab identified retinal ganglion cell (RGC) synapse loss within the lateral geniculate nucleus (LGN), leading to visual dysfunction. This synapse loss is mediated by microglia—the innate immune cells of the brain—engulfing and eliminating RGC terminals prior to significant demyelination, axonal degeneration, or neuronal cell death. More recently, we have also identified a partial recovery of synapses in the LGN during phases of repair, though regulatory factors underlying this synaptic restoration remain unknown. Neuronal activity is a powerful regulator of microglia-synapse interactions and plays an essential role in synaptic elimination and formation during healthy visual system development. Thus, we hypothesize that repair of RGC synapses in the LGN is governed by RGC activity. To test this, RGC activity was experimentally manipulated in the commonly used MS-relevant cuprizone (CPZ) mouse model. Here we will present new data assessing the impact RGC activity has on synaptic repair and visual circuit function using comprehensive functional and histological analyses, including optomotor testing of visual acuity and immunohistochemistry. Furthermore, we identify glia-derived secreted synaptic regulators that may contribute to synaptic recovery. By investigating the molecular mechanisms governing the repair of synaptic circuits in demyelinating disease, we aim to uncover novel therapeutic targets for the treatment of MS and related neurodegenerative diseases in which synaptic loss and dysfunction comprise hallmark pathologies.

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