BIOGRAPHICAL SKETCH

NAME: Seyfried, Nicholas Thomas

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

POSITION TITLE: Associate Professor of Biochemistry and Neurology

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date MM/YYYY	FIELD OF STUDY
Boston College, Chestnut Hill MA	B.S.	09/95-05/99	Biochemistry
University of Oxford, United Kingdom	PhD	09/01-12/04	Biochemistry
University of Georgia, Athens GA	postdoc	12/04-12/06	Mass Spectrometry
Emory University School of Medicine, Atlanta GA	postdoc	12/06-08/10	Proteomics

A. Personal Statement

Dr. Seyfried received his PhD in Biochemistry from the University of Oxford (United Kingdom) in 2005. After postdoctoral training at the University of Georgia and Emory University School of Medicine, he joined the Departments of Biochemistry and Neurology as a faculty member in 2011. He is a member of the Emory Goizueta Alzheimer's Disease Research Center and Center for Neurodegenerative Diseases and has published over 100 peer-reviewed manuscripts utilizing mass spectrometry-based proteomics for basic and translational research discoveries with an emphasis on Alzheimer's Disease. Currently the major research goals of the Seyfried lab is to utilize quantitative proteomics methodologies to better understand the pathogenesis of Alzheimer's Disease (AD) and other neurodegenerative diseases. As part of the National Institutes of Health (NIH) Accelerating Medicines Partnership for Alzheimer's Disease (AMP-AD) consortium, his team leverages the strengths of a national team of collaborating investigators to couple advanced transcriptomics, proteomics and metabolomics with bioinformatics approaches, to nominate new drug targets for AD treatment. His group has developed a high throughput pipeline to process and analyze ~2,000 human postmortem brain tissues by both label-free quantitative mass spectrometry (Johnson *et. al., Nat Med.* 2020) and multiplex isobaric tandem mass tags (TMT), the latter pipeline generates proteomes of ~10,000 proteins in depth (Ping *et. al.,* 2018 *Scientific Data* and Higginbotham *et. al.,* 2020 *Science Advances*). Systems biology approaches such as Weighted Co-expression Network Analysis (WGCNA) are currently being used by his group to classify the brain proteome into biologically meaningful modules related to clinicopathological phenotypes. These networks can be integrated with CSF and plasma proteomic profiles to nominate new brain-derived biomarkers that can identify individuals in the asymptomatic stages of AD prior to any evidence of cognitive decline.

B. Positions and Honors

1999-2001 Research Assistant, Department of Neurosurgery, Harvard Medical School, Boston, MA
2011- Assistant Professor, Department of Biochemistry, Emory School of Medicine, Atlanta, GA
2011- Scientific Director, Emory NINDS-Neuroscience Core Facility (ENNCF) for Proteomics
2014- Scientific Director, Emory Integrated Proteomics Core
2018- Associate Professor (tenured), Departments of Biochemistry and Neurology, Emory School of Medicine

Honors:

2003-04 Arthritis Research Campaign D.Phil. Studentship
2004 British Society for Matrix Biology Travel Award
2007-09 NIH T32 NRSA Fellowship in Translational Neurology
2009-10 NIH F32 NRSA Fellowship (National Institute of Aging)

Other Experience and Professional Memberships:

2005- American Society for Mass Spectrometry
2007- Society for Neuroscience
2012- American Society for Neurochemistry
2016- USHUPO
2007-2008 GeorgiaBio Emerging Leaders Network (ELN) business relations committee
2010-2011 ad hoc reviewer for *Journal of Proteome Research*
2011 ad hoc reviewer for *Journal of Biological Chemistry*
2011 ad hoc reviewer for *PlosOne*
2012 ad hoc reviewer for *Human Molecular Genetics*

2014 ad hoc reviewer for *Proteomics*
2014 ad hoc reviewer for *Journal of Proteomics*
2011- ad hoc reviewer Alzheimer's Association NIRGs
2015 ad hoc reviewer for NIH EBIT study section grant applications
2018- ad hoc reviewer for NIH NIA SEP Alzheimer's Disease Study Sections

C. Contributions to Science

1. **RNA binding protein aggregation and splicing defects in AD and related neurodegenerative diseases**. Over the past 15 years I have used large scale quantitative proteomics approaches to systematically assess characterize RNA-binding protein aggregation and post-translational modifications (PTMs) that underlie neurodegenerative diseases. As a post-doc I was awarded an F32 NRSA to characterize PTMs on TAR DNA-binding protein 43 (TDP-43), the major aggregated protein in frontotemporal dementia (FTD) and amyotrophic lateral sclerosis. I showed that aggregated TDP-43 is not only directly ubiquitinated, but also SUMOylated in cells. I also defined the biochemical and cellular properties of an alternatively spliced short isoform of TDP43. More recently, our group has shown that numerous spliceosome proteins, including U1-70K, aggregate in AD in close association with tau neurofibrillary tangles. Splicing defects were also found significantly elevated in AD brain, further supporting the role of spliceosome loss-of-function in AD. Our recent evidence indicates that intrinsically disordered basic-acidic motifs in low complexity (LC) domains are necessary for U1-70K aggregation and association with Tau in AD brain.
    a. **Seyfried NT**, Gozal YM, Dammer EB, Xia Q, Duong DM, Cheng D, Lah JJ, Levey AI, Peng J. Multiplex SILAC analysis of a cellular TDP-43 proteinopathy model reveals protein inclusions associated with SUMOylation and diverse polyubiquitin chains. *Mol Cell Proteomics.* 2010 Apr;9(4):705-18. PMCID: PMC2860236.
    b. Diner I, Hales CM, Bishof I, Rabenold L, Duong DM, Yi H, Laur O, Gearing M, Troncoso J, Thambisetty M, Lah JJ, Levey AI, **Seyfried NT**. Aggregation properties of the small nuclear ribonucleoprotein U1-70K in Alzheimer disease. J Biol Chem. 2014 Dec 19;289(51):35296-313. PMCID: PMC4271217.
    c. Bishof, I., Dammer, EB., Duong, DM., Gearing, M., Lah, JJ, Levey, AI, and **Seyfried, NT**. (2018) RNA-binding proteins with basic-acidic dipeptide (BAD) domains self-assemble and aggregate in Alzheimer's disease. J Biol Chem. 2018 Jul 13;293(28):11047-11066. PMCID: PMC6052236
    d. Johnson ECB, Dammer EB, Duong DM, Yin L, Thambisetty M, Troncoso JC, Lah JJ, Levey AI, **Seyfried NT**. Deep proteomic network analysis of Alzheimer's disease brain reveals alterations in RNA binding proteins and RNA splicing associated with disease. Mol Neurodegener. 2018 Oct 4;13(1):52. PMCID: PMC6172707.

2. **Understanding post-translational modifications and genetic variation in AD and related neurodegenerative diseases.** My group has both independently and worked collaboratively to identify and quantify novel PTMs using mass spectrometry-based proteomics. These studies have revealed novel protein isoforms of key substrates including sites of acetylation, ubiquitination, phosphorylation and proteolysis that have led to new mechanisms and drug targets in neurodegenerative disease. We have also utilized an integrative proteogenomic approach to generate personalized protein databases from whole exome sequencing data to identify rare coding variants in the human brain proteome, which allows us to measure allele specific changes in protein abundance using isotope dilution mass spectrometry.
    a. Dammer EB, Duong DM, Diner I, Gearing M, Feng Y, Lah JJ, Levey AI, **Seyfried NT**. Neuron enriched nuclear proteome isolated from human brain. J Proteome Res. 2013 Jul 5;12(7):3193-206. PMCID: PMC3734798.
    b. Dammer EB, Lee AK, Duong DM, Gearing M, Lah JJ, Levey AI, **Seyfried NT**. Quantitative phosphoproteomics of Alzheimer's disease reveals cross-talk between kinases and small heat shock proteins. *Proteomics.* 2015 Jan;15(2-3):508-19. doi: 10.1002/pmic.201400189. PubMed PMID: 25332170; PubMed Central PMCID: PMC4404162.
    c. Wingo TS, Duong DM, Zhou M, Dammer EB, Wu H, Cutler DJ, Lah JJ, Levey AI, **Seyfried NT** Integrating Next-Generation Genomic Sequencing and Mass Spectrometry to Estimate Allele-Specific Protein Abundance in Human Brain. *J Proteome Res*. 2017 Sep 1;16(9):3336-3347.
    d. Abreha MH, Dammer EB, Ping L, Zhang T, Duong DM, Gearing M, Lah JJ, Levey AI, **Seyfried NT**. Quantitative Analysis of the Brain Ubiquitylome in Alzheimer's Disease. Proteomics. 2018 Oct;18(20):e1800108. PMCID: PMC6283072.

3. **Integrated proteomic network approaches to define therapeutic targets and biomarkers in AD and related neurodegenerative diseases** Currently my group is generating quantitative proteomic data to all the U01 NIH grants in the country that were awarded to identify and develop new therapeutic targets for AD as part of the NIH Accelerating Medicine Partnership Alzheimer's Disease (AMP-AD) Consortium. In the AMP-AD working groups we develop novel system level approaches to pinpoint common disease mechanisms linking AD pathology and GWAS targets with cognitive decline and resiliency. Towards this end, my team has developing systems level approaches to better understand proteomic changes that co-occur with AD and related neurodegenerative diseases.
    a. **Seyfried NT**, Dammer EB, Swarup V, Nandakumar D, Duong DM, Yin L, Deng Q, Nguyen T, Hales CM, Wingo T, Glass J, Gearing M, Thambisetty M, Troncoso JC, Geschwind DH, Lah JJ, Levey AI. A Multi-network Approach Identifies Protein-Specific Co-expression in Asymptomatic and Symptomatic Alzheimer's Disease. *Cell Syst.* 2016 Dec 14. pii: S2405-4712(16)30370-2. PMCID: PMC5269514
    b. Ping, L, Duong, D, Yin, L, Gearing, M, Lah, JJ, Levey, A.I, and **Seyfried, NT**.Global Quantitative Analysis of the Human Brain Proteome in Alzheimer's and Parkinson's Disease. *Scientific Data*. 2018 Mar 13;5:180036. PMCID: PMC5848788
    c. Higginbotham, L., Ping, L., Dammer, E. B., Duong, D. M., Zhou, M., Gearing, M., Johnson, E. C. B., Hajjar, I., Lah, J. J., Levey, A. I., and **Seyfried, N. T.** Integrated Proteomics Reveals Brain-Based Cerebrospinal Fluid Biomarkers in Asymptomatic and Symptomatic Alzheimer's Disease. *Sci Adv 2020 Oct 21;6:eaaz9360.* PMID: 33087358
    d. Johnson ECB, Dammer EB, Duong DM, Ping L, Zhou M, Yin L, Higginbotham LA, Guajardo A, White B, Troncoso JC, Thambisetty M, Montine TJ, Lee EB, Trojanowski JQ, Beach TG, Reiman EM, Haroutunian V, Wang M, Schadt E, Zhang B, Dickson DW, Ertekin-Taner N, Golde TE, Petyuk VA, De Jager PL, Bennett DA, Wingo TS, Rangaraju S, Hajjar I, Shulman JM, Lah JJ, Levey AI, **Seyfried NT**. Large-scale proteomic analysis of Alzheimer's disease brain and cerebrospinal fluid reveals early changes in energy metabolism associated with microglia and astrocyte activation. *Nat Med.* 2020 May;26:769-780. Epub 2020 Apr 13 PMID: 32284590.

Complete List of Published Manuscripts (108 total) in MyBibliography:
https://www.ncbi.nlm.nih.gov/sites/myncbi/nicholas.seyfried.1/bibliography/41152401/public/?sort=date&direction=ascending.

D. Research Support
Ongoing Research Support

R01AG053960 (MPI Shulman and Seyfried) 9/15/2016–4/30/2021 NIH/NIA
Tau-Spliceosome Interactions in Alzheimer's disease
In this study we will leverage clinicopathologic samples from the Religious Order Study (ROS) and Rush Memory and Aging Project (MAP), to investigate whether U1 or other spliceosomal complexes are disrupted in AD. To achieve this goal we will first deploy a targeted, quantitative proteomic assay for ~200 proteins, including all known spliceosomal components and related non-spliceosomal RNA-binding proteins, in detergent insoluble cortical fractions.
Role: Consortium MPI

R01AG061800 (MPI Herskowitz and Seyfried) 09/01/2018 – 04/30/2023 NIH/NIA
Identifying therapeutic targets that confer synaptic resilience to Alzheimer's disease
The goal of this project is to use MS based proteomics and network approaches of the synaptosomes to define signaling pathways linked to cognitive resiliency.
Role: Consortium MPI

R01AG057339 (MPI Botas, Shulman, Liu and Seyfried) 09/15/2017 - 05/31/2022 NIH/NIA
Functional Dissection of Alzheimer's Disease Networks in Drosophila: from Association to Causal Modulators of Age-Dependent Neurodegeneration
To goal of this proposal is to use Protein co-expression network analysis to prioritize networks of proteins related to aging and tau toxicity and integrative network analysis will be used to assess overlap between the proteome and transcriptome. Finally, a targeted mass spectrometry approach termed Selective Reaction Monitoring (SRM)

will be employed to validate the protein levels of key drivers related to aging and/or Tau phenotypes in the fly proteome.
Role: Consortium MPI

1RF1AG062181 (MPI Cummings and Seyfried) 09/30/2018 – 06/30/2023 NIH/NIA
Glycoproteomics & Glycosylation Code of the Brain in Asymptomatic and Symptomatic Alzheimer's Disease"
The goal of this project is to use MS based approaches to characterize the glycome in Alzheimer's disease.
Role: Consortium MPI

U01AG061357 (MPI Levey, Seyfried and Shulman) 09/30/2018- 08/31/2023 NIH/NIA
AMP-AD Brain Proteomic Network Enhancement, Validation, and Translation into CSF Biomarkers
The goal of this proposal is to use proteomics to define new targets and biomarkers in Alzheimer 's disease.
Role: MPI

U01AG061356 (De Jager) 09/01/2020 – 08/31/2022 NIH/NIA
Multi-omic network-directed proteoform discovery, dissection and functional validation to prioritize novel AD therapeutic targets
The interactomes and proteoforms of approximately 12 nominated AMP-AD targets coimmunoprecipitated to be analyzed by LC-MS/MS. This will be performed using an Orbitrap Fusion mass spectrometer housed in the Emory Integrated Proteomics Core.
Role: Consortium PI

RF1AG057470 (MPI Hajjar & Seyfried) 09/15/2017-06/30/2021 NIH/NIA
Building a high-resolution multi-omic AD interactome with the AMP-AD and M2OVE-AD Projects
The goal is to develop a novel plasma protein biomarker platform for AD by deeply profiling the proteomes of matched brain and plasma samples from the same cases, linking the protein networks to the extensive clinical, pathological, and molecular data available in the Accelerating Medicine Partnership for AD (AMP-AD) to nominate candidate plasma markers and validate their performance in several independent cohorts.
Role: MPI

R01MH117292 (Ressler) 07/25/2018 – 4/30/2023 NIH/NIMH
Understanding PTSD through Postmortem Targeted Brain Multiomics
The proteomes of 900 human postmortem brain tissues (300 subjects) from three brain regions (amygdala, hippocampus and prefrontal cortex) will be analyzed by quantitative mass spectrometry based proteomics.
Role: Consortium PI

U54AG065187 (Levey) 09/01/2019 – 08/31/2024 NIH/NIA
Open Drug Discovery Center for Alzheimer's Disease/ Core-001 (002) Bioinformatics
The goal of this proposal is to catalyze drug development by developing and openly distributing high-quality reagents for evaluation of a diverse set of next generation AD drug targets across the research community.
Role: Co-Investigator

R01AG015819 (Bennett) 07/15/2019 – 04/30/2024 NIH/NIA
Risk Factors, Pathology, and Clinical Expressions of AD
The goal of this project is to analyze 750 human postmortem brain tissues by quantitative mass spectrometry. The approach will utilize a chemical labeling strategy termed Tandem Mass Tags (TMTs).
Role: Consortium PI

P01NS084974 (Petrucelli) 04/01/2020 – 03/31/2025 NIH/NINDS
Pathobiology of Neurodegeneration in C9ORF72 Repeat Expansion
The Emory proteomics team, led by Dr. Seyfried, will be responsible for all work done as described in Project 3, including proteomics of human
and mouse tissues.
Role: Consortium Co-I