BIOGRAPHICAL SKETCH

NAME Eric B. Dammer	POSITION TITLE Postdoctoral Fellow
eRA COMMONS USER NAME EDAMMER	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Florida Gulf Coast University (FGCU)	B.A.	01/01-08/03	Liberal Arts, Molecular Biology focus
Georgia Institute of Technology (Georgia Tech)	PhD	09/03-12/08	Biology, Molecular Genetics focus
Emory University School of Medicine	postdoc	09/08-current	Mass Spectrometry and Neuroproteomics

A. Personal Statement

Dr. Dammer has 10 years of biochemistry, molecular biology, and mass spectrometry experience. As a graduate and since beginning his postdoc in 2008, he has routinely performed mass spectrometry experiments and validation and interpretation of mass spectrometric data via design and execution of varied molecular biological and biochemical experiments. As a postdoc at Emory, he has been involved in a number of projects related to neurodegeneration and neuroproteomics. For example, one project resulting in a JBC publication describes protein quality control mediated by ubiquitin conjugation and proteolytic stress relevant to neurodegeneration and developing methods to measuring ubiquitin linkages by mass spectrometry to determine deficiencies in protein disposal or refolding capacity in Alzheimer Disease human postmortem brain. Another project involved defining the sites and effects upon aggregation of the amyotrophic lateral sclerosis and frontotemporal dementia proteinopathic protein TDP-43 and associated coaggregating proteins, published in *PLoS One*. The depth of these projects, their employed methods, and the hypotheses tested, in combination with their comparative breadth and the increasing momentum towards high-impact publications have established Eric as capable in the field of neuroproteomics.

In other projects, Dr. Dammer will perform in-gel digests and LC-MSMS analyses of human control, asymptomatic AD, MCI, and AD cases. He will use bioinformatics approaches to define specialized proteomic databases and search MS/MS spectra against these databases to identify novel mis-spliced protein products in AD at the peptide level. He will validate these products at the transcript level by PCR and quantify at the peptide level using synthetic standards. He will also perform all *in situ* hybridization studies for the analysis of U1 snRNA in tissue as well as perform functional knockdown experiments in cell lines. Finally, he will communicate closely with Phil De Jager to analyze RNA-seq data and generate custom built protein databases based on these data.

B. Positions and Honors

Positions:

1998-2000 Operations Manager, Moneyline Telerate, New York, NY
2002 Tutor and Teaching Assistant, Organic Chemistry, Florida Gulf Coast Univ., Fort Myers, FL

Academic and Professional Honors

2007 Best Presentation, College of Sciences, 3rd Ann. Graduate Student Gvmt. Research Symposium
2006 Travel Award, Keystone Symposia Nuclear Receptors Conference
2003-07 Georgia Tech President's Fellowship
2002 HHMI Summer Internship at Georgia Tech School of Biology (Dr. Nael A. McCarty, PI)
2002 FGCU Campbell Engineering Scholarship
2002 Golden Key National Honor Society Inductee

C. Publications

Peer-Reviewed Publications

1. Urs AN, **Dammer EB**, Sewer MB. "Sphingosine Regulates the Transcription of CYP17 by Binding to Steroidogenic Factor-1." *Endocrinology* 147(11): 5249-58. 2006. PMID: 16887917

2. Urs AN, **Dammer EB**, Kelly S, Wang E, Merrill AH Jr, Sewer MB. "Steroidogenic Factor-1 Is a Sphingolipid Binding Protein." *Mol Cell Endocrinol* 265-266: 174-8. 2007. PMCID: PMC1850975

3. **Dammer EB**, Leon A, Sewer MB. "Coregulator Exchange and Sphingosine-Sensitive Cooperativity of Steroidogenic Factor-1, General Control Nonderepressed 5, p54, and p160 Coactivators Regulate Cyclic Adenosine 3',5'-Monophosphate-Dependent Cytochrome P450c17 Transcription Rate." *Mol Endocrinol* 21(2): 415-38. 2007. PMID: 17121866

4. **Dammer EB**, Sewer MB. "Phosphorylation of CtBP1 by PKA Modulates Induction of CYP17 by Stimulating Partnering of CtBP1 and 2." *J Biol Chem* 283(11): 6925-34. 2008. PMCID: PMC2730192

5. Seyfried NT, Gozal YM, **Dammer EB**, Xia Q, Duong D, 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* 9(4): 705-18. 2010. PMCID: PMC2860236

6. **Dammer EB**, Xu P, Seyfried NT, Rees HD, Gearing M, Lah JJ, Levey AI, Peng J. "Polyubiquitin Linkage Profiles in Three Models of Proteolytic Stress Suggest Etiology of Alzheimer Disease." *J Biol Chem* 286(12): 10457-65. 2011. PMCID: PMC3060499

7. Sephton CF, Cenik C, Kucukural A, **Dammer EB**, Cenik B, Han YH, Dewey CM, Roth FP, Herz J, Peng J, Moore MJ, Yu G. "Identification of Neuronal RNA Targets of TDP-43-containing Ribonucleoprotein Complexes." *J Biol Chem* 286(2): 1204-15. 2011. *F1000 "must read."* PMCID: PMC3020728

8. Gozal YM, **Dammer EB**, Duong DM, Cheng D, Gearing M, Rees HD, Peng J, Lah JJ, Levey AI. "Proteomic Analysis of Hippocampal Dentate Granule Cells in Frontotemporal Lobar Degeneration: Application of Laser Capture Technology." *Front Neurodegen* 2(art. 24). 2011. PMCID: PMC3085134

9. **Dammer EB**, Fallini C, Gozal YM, Rossoll W, Xu P, Duong DM, Lah JJ, Levey AI, Peng J, Bassell GJ, Seyfried NT. "Coaggregation of RNA-binding Proteins in a Cellular Model of TDP-43 Proteinopapthy with Selective RGG Motif methylation and RRM Domain Ubiquitination." *PLoS One* 7(6): e38658. 2012. PMCID: PMC3380899

10. Donovan LE, Higginbotham L, **Dammer EB**, Gearing M, Rees H, Xia Q, Duong D, Seyfried NT, Lah JJ, Levey AI. "Analysis of a Membrane Enriched Proteome from Post-mortem Human Brain Tissue in Alzheimer's Disease." *Proteomics Clin Appl* 6(3-4): 201-11. 2012. PMCID: PMC3338199

11. Seyfried NT, Gozal YM, Donovan LE, Herskowitz JH, **Dammer EB**, Xia Q, Ku L, Chang J, Duong DM, Rees HD, Cooper DS, Glass JD, Gearing M, Tansey MG, Lah JJ, Feng Y, Levey AI, Peng J. "Quantitative Analysis of the Detergent-Insoluble Brain Proteome in Frontotemporal Lobar Degeneration Using SILAC Internal Standards." *J Proteome Res* 11(5): 2721-38. 2012. PMCID: PMC3357000

12. Wu F, Wu J, Nicholson AD, Echeverry R, Haile WB, Catano M, An J, Lee AK, Duong D, **Dammer EB**, Seyfried NT, Tong FC, Votaw JR, Medcalf RL, Yepes M. "Tissue-type Plasminogen Activator Regulates the Neuronal Uptake of Glucose in the Ischemic Brain." *J Neurosci* 32(29) 9848-58. 2012. PMCID: PMC3437989

13. Herskowitz JH, Gozal YM, Duong DM, **Dammer EB**, Gearing M, Ye K, Lah JJ, Peng J, Levey AI, Seyfried NT. "Asparaginyl Endopeptidase Cleaves TDP-43 in Brain." *Proteomics* 12(15-16): 2455-63. 2012. PMID: 22718532

14. Fan F, Nie S, **Dammer EB**, Duong DM, Pan D, Ping L, Zhai L, Wu J, Hong X, Qin L, Xu P, Zhang Y-H. "Protein Profiling of Active Cysteine Cathepsins in Living Cells Using an Activity-Based Probe Containing a Cell-Penetrating Peptide." *J Proteome Res* 11(12): 5763-72. 2012. PMID: 23082807

15. Li D, **Dammer EB**, Sewer MB. "Resveratrol Stimulates Cortisol Biosynthesis by Activating SIRT-Dependent Deacetylation of $P450_{scc}$." *Endocrinology* 153(7): 3258-68. 2012. PMCID: PMC3380297

16. Li D, **Dammer EB**, Lucki NC, Sewer MB. "cAMP-stimulated Phosphorylation of Diaphanous 1 Regulates Protein Stability and Interaction with Binding Partners in Adrenocortical Cells." *Mol Biol Cell* 24(6): 848-57. 2013. PMCID: PMC3596254

17. Willmund F, Del Alamo M, Pechmann S, Chen T, Albanèse V, **Dammer EB**, Peng J, Frydman J. "The Cotranslational Function of Ribosome-associated Hsp70 in Eukaryotic Protein Homeostasis." *Cell* 152(1-2): 196-209. 2013. PMID: 22332755

18. Kallappagoudar S, **Dammer EB**, Duong DM, Seyfried NT, Lucchesi JC. "Expression, Purification and Proteomic Analysis of Recombinant Histone H4 Acetylated at Lysine 16." *Proteomics* 13(10-11): 1687-91. 2013. PMID: 23554095

19. Donovan LE, **Dammer EB**, Duong DM, Hanfelt JJ, Levey AI, Seyfried NT, Lah JJ. "Exploring the Potential of the Platelet Membrane Proteome as a Source of Peripheral Biomarkers for Alzheimer's Disease." *Alz Res Ther* 5(3). *Published online June 2013.* PMID: 23764030

20. **Dammer EB**, Duong DM, Diner I, Gearing M, Feng Y, Lah JJ, Levey AI, Seyfried NT. "A Neuron Enriched Nuclear Proteome Isolated from Human Brain." *J Proteome Res* 12(7): 3193-206. 2013. PMCID: PMC3734798

21. Wu F, Nicholson AD, Haile WB, Torre E, An J, Chen C, Lee AK, Duong DM, **Dammer EB**, Seyfried NT, Tong FC, Votaw JR, Yepes M. "Tissue-type Plasminogen Activator Mediates Neuronal Detection and Adaptation to Metabolic Stress." *J Cereb Blood Flow Metab*. *Published online Jul 24, 2013*. PMID: 23881246

22. Bai B, Hales CM, Chen P-C, Gozal YM, **Dammer EB**, Fritz JJ, Wang X, Xia Q, Duong DM, Street C, Cantero G, Cheng D, Jones DR, Wu Z, Li Y, Diner I, Heilman CJ, Rees HD, Wu H, Lin L, Szulwach KE, Gearing M, Mufson EJ, Bennett DA, Montine TJ, Seyfried NT, Wingo TS, Sun YE, Jin P, Hanfelt J,

Willcock DM, Levey AI, Lah JJ, Peng J. “U1 Small Nuclear Ribonucleoprotein Complex and RNA Splicing Alterations in Alzheimer’s Disease.” *Proc Natl Acad Sci USA. Accepted Aug 13, 2013*.

Reviews in Peer Reviewed Journals

23. Sewer MB, **Dammer EB**, Jagarlapudi S. “Transcriptional Regulation of Adrenocortical Steroidogenic Gene Expression.” *Drug Metab Rev* 39(2): 371-88. 2007. PMID: 17786627

24. Sewer MB, Li D, **Dammer EB**, Jagarlapudi S, Lucki N. “Multiple Signaling Pathways Coordinate CYP17 Gene Expression in the Human Adrenal Cortex.” *Acta Chim Slov* 55(1): 53-7. 2008. PMCID: PMC2809372

25. **Dammer EB**, Peng J. “At the Crossroads of Ubiquitin Signaling and Mass Spectrometry: the First Conference on Proteomics of Protein Degradation and Ubiquitin Pathways.” *Expert Rev Proteomics*, invited review. 2010. PMID: 20973637

Meeting Abstracts

1. **Dammer EB**, Seyfried NT, Xu P, Gozal YM, Gearing M, Lah JJ, Levey AI, Peng J (2009). “Selected Reaction Monitoring (SRM) of Ubiquitin Isopeptide Linkages in Neurodegenerative Disease.” ASMS, Philadelphia, PA. *Selected for presentation.*

2. **Dammer EB**, Xu P, Seyfried NT, Duong DM, Gearing M, Rees HD, Lah JJ, Levey AI, Peng J (2010). “Profiling PolyUb Signatures of Insufficient Proteasome, Lysosome, and Chaperone Quality Control.” PPDUP, Vancouver, BC.

3. **Dammer EB**, Xu P, Seyfried NT, Rees HD, Gearing M, Lah JJ, Levey AI, Peng J. “Polyubiquitin Linkage Profiles in Models of Proteolytic Stress Suggest Alzheimer Disease Etiology.” CNHUPO, Hangzhou, Zhejiang, China. *Selected for presentation.*

D. Funding

ACTIVE

09/30/2011 - 09/29/2013 Ruth Kirschstein NRSA F-32 AG038259

Defining Mechanisms of TDP-43 Ubiquitination for Quality Control and Aggregation

Neurodegeneration in frontotemporal lobar dementia with ubiquitinated inclusions (FTLD-U), amyotrophic lateral sclerosis (ALS), and other delayed-onset diseases associated with degeneration of aging neurons involves a deficit in the degradation of the TAR DNA binding protein (TDP-43). This deficit is apparent through the characteristic pathology of a cross-section of neurodegenerative diseases, i.e., accumulation and aggregation of protein inclusions positive for TDP-43 and ubiquitin (Ub) in ALS, FTLD-U, and a large fraction of Alzheimer's Disease (AD) and Parkinson's Disease (PD) cases. Ub is a small protein conjugated singly or in polymeric chains to substrate proteins like TDP-43 that has the capacity to alter substrate fate, e.g. degradation, (in)activation, or relocation out of specific cellular compartments or protein complexes. The proposed research identifies the determinants of TDP-43 degradation, and determines the role of K63-linked polyubiquitin in rerouting of TDP-43 from degradation pathways to disease-characteristic aggregates. Half-life studies in cortical neurons and glia and in human cell lines measure the contributions of cellular alternatives for protein degradation, the proteasome and lysosome, to the degradation kinetics of endogenously expressed TDP-43. In addition, K63-linked Ub chains on TDP-43 and their association with the cell's quality control and aggregation-control machinery are identified by experiments in a cell line engineered to express modified Ub. Components of cellular quality control machinery have been shown to engage TDP-43 in neurodegenerative tissue and in models of neurodegeneration, particularly those which test the effects of insufficient proteasome or lysosome activity on substrates such as TDP-43. This insufficiency may passively develop in neurons during the course of aging or may develop due to environmental factors that affect sporadic neurodegeneration. Significant quantitative differences in interactions between TDP-43 and the Ub-dependent proteasome, lysosome, and quality control systems of cells in disease tissue will be identified. Interactions relevant to disease progression (biomarkers) or etiology (therapeutic targets) are to be confirmed by immunohistochemical staining in postmortem tissue from FTLD-U and ALS neurodegenerative disease. Finally, biochemical assays will be employed to identify specific therapeutic target(s) that deposit K63-linked Ub chains onto TDP-43; K63 Ub linkages significantly increase in neurodegenerative disease and published models of TDP-43 proteinopathy. ALS-specific mutations of TDP-43 will be tested for changes in the propensity of the protein to interact with identified interaction partners, particularly the Ub ligase that deposits K63-linked Ub chains onto TDP-43. The proposed measurements of alternative Ub chains and identification of novel disease-related proteins will rely on mass spectrometry methods and software developed by the PI and his mentors at the Emory proteomics facility and Center for Neurodegenerative Disease, where the proposed research takes place.

COMPLETED

07/01/2010 – 06/30/2011 T-32 NS-007480

Training in Translational Research in Neurology

To further the understanding of protein oligomerization, aggregation, and associated dysregulation of cellular processes relevant to AD, I proposed to first confirm that the U1 snRNP complex is involved in the development of AD pathology, including neurofibrillary tangles either containing microtubule associated protein Tau (MAPT) pathology, or concurrent with this pathology. I hypothesized (1) that U1 snRNP loss of function is associated with cytoplasmic retention and development of U1 component-containing tangles, as well as biochemical insolubility in MCI (Table 1) not yet associated with visible pathology. (2) This change in the function of U1, the first essential spliceosome component complex in the major eukaryotic splicing pathway (affecting 98% of splicing events), may lead to increased exon inclusion or skipping in alternative splicing targets including the pre-mRNA for the protein Tau or U1-70k.