Presentations

Poster Presentations:
Society for Neuroscience annual meeting, Washington D.C. November 2011.

Oral Presentation:
December 2012. Title: Biomarkers of central nervous system injury in mouse models of Alexander disease. Molecular and Genetic Sciences Group, Madison, WI.

Honors & Awards

2008-2009, Wayne and Jean Roper Distinguished Graduate Fellowship, University of Wisconsin

2001-2003, James Scholar, University of Illinois

Fall 2001, Fall 2002, Dean's List, University of Illinois

2001, The National Dean's List, University of Illinois

2001, Alpha Lambda Delta for First Year Students, University of Illinois

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The University of Wisconsin - Madison
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Cellular and Molecular Pathology

Paige Jany

Program of the Thesis Defense Seminar for the
Degree of Doctor of Philosophy
in Cellular and Molecular Pathology

"Efficacy of GFAP as a biomarker for Alexander disease and estrogenic regulation of GFAP"

Wednesday, May 22, 2013 – 1pm
John D. Wiley Conference Center
T216, Second Floor, North Tower
Waisman Center

Research conducted in the lab of
Albee Messing, VMD, PhD
Department of Comparative Biosciences

Paige Jany's Thesis Abstract

Efficacy of GFAP as a biomarker for Alexander disease and estrogenic regulation of GFAP

Paige Jany
Under the supervision of
Professor Albee Messing, VMD, PhD
at the University of Wisconsin-Madison

Alexander disease (AxD) is a rare and fatal neurodegenerative disorder caused by mutations in glial fibrillary acidic protein (GFAP), which leads to GFAP accumulation above an unknown toxic threshold. There is no cure for AxD, but reduction of GFAP may alleviate AxD patient symptoms. In anticipation of future drug therapies, we explored the potential of GFAP as a biomarker for analysis of drug efficacy in mouse models of AxD and AxD patients. In chapter 2, we investigated two independent measures of GFAP expression in AxD mouse models: a genetic reporter of promoter activity and quantification of GFAP protein directly in a manner that could also be employed in human studies. Using a reporter mouse line which expresses firefly luciferase under the control of the murine *Gfap* promoter, we found that luciferase activity reflected the regional CNS variability of *Gfap* mRNA in *Gfap*$^{+/+}$ mice, and increased in a mouse model of AxD. We also quantified GFAP protein in CSF from three different AxD mouse models and found GFAP levels increased in all models. In chapter 3, we analyzed GFAP protein in CSF and plasma from AxD patients, finding GFAP was significantly elevated in both CSF and plasma of AxD patients compared with controls. Taken together, we found luciferase activity in the brain and GFAP in both CSF and plasma accurately reflected *Gfap* promoter activity and protein levels respectively, suggesting both are good biomarkers for AxD. In chapter 4, we analyzed the potential GFAP regulatory effects of estradiol (E2). A previous drug screen of FDA-approved drugs revealed E2 decreased *Gfap* promoter activity by 26%. In a mouse model of AxD, we found minimal changes in GFAP expression resulting from either surgical or pharmacological manipulation of estradiol levels. In addition, no fluctuation in GFAP expression was evident during the natural variations in endogenous estrogens occurring during the estrous cycle. These studies suggest caution in the implementation of estrogen-based treatments for AxD. Overall, the conclusions of the work described in this report reveal GFAP is a useful biomarker for AxD and can be utilized in future clinical trials to determine drug efficacy.

Publications

Messing, A., **P.L. Jany**, G.E. Agosta, W.S. Benko, J.C. Eickhoff, F. Eichler, D. Janigro, W. Köehler, J.M. Ness, D. Pareyson, V. Puvenna, D.L. Renaudand, W. Rizzo, A. Vanderver, S. Mar, J. Zempel, and M.S. van der Knaap, Plasma and cerebrospinal fluid levels of GFAP in Alexander disease. (In Progress).

Jany, P.L. and A Messing. Estrogens and GFAP expression in a mouse model of Alexander Disease. (In Progress).

Jany, P.L., T.L. Hagemann, and A. Messing. GFAP expression as an indicator of disease severity in mouse models of Alexander disease. ASN Neuro, 2013.

Cunningham, R., **P.L. Jany**, A. Messing and L. Li. Protein changes in immunodepleted cerebrospinal fluid from a transgenic mouse model of Alexander disease detected using mass spectrometry. J Proteome Res, 2013. 12(2): p. 719-28.