Name: Erin McMillan

Email: emcmillan@wisc.edu

Major Professor: Dr. Anjon Audhya

Degree Objective: Ph.D. Endocrinology and Reproductive Physiology

Background: BS Zoology, University of Wisconsin-Madison

MBA, California State University, San Marcos

Current Research Project:

Secretory proteins, which are predicted to account for nearly one third of all proteins that are translated, are delivered to the *cis*-Golgi apparatus from the endoplasmic reticulum (ER) via coat protein complex II (COPII)-coated vesicles. My lab has shown that a key regulator of the secretory pathway is Trk-fused gene (TFG), which localizes to sites of COPII vesicle biogenesis on the ER, facilitates the formation and anterograde transport of COPII vesicles, and maintains ER morphology. A major goal of my work is to better understand the mechanisms by which TFG functions in the early secretory pathway. Efficient protein secretion is required for normal endocrine signaling, as many hormones, including luteinizing hormone, follicle stimulating hormone, prolactin, and insulin, must be packaged into COPII-coated vesicles and transported through the Golgi apparatus into secretory granules, prior to their release into the bloodstream. Additionally, efficient protein secretion is critical during many stages of pregnancy. For example, decidual cells and the endometrial glands secrete growth factors and various other factors necessary for the implantation of the embryo. Thus, my work will have a broad impact on the fields of endocrinology and reproductive physiology.

Interestingly, mutations in TFG have been identified in several neurodegenerative disorders, including childhood-onset hereditary spastic paraplegia (HSP). HSP refers to a group of inherited disorders, characterized by progressive weakness and spasticity of the legs due to degeneration of upper motoneuron axons in the corticospinal tract. Individuals with HSP may also experience degradation of the optic nerve, ataxia, peripheral neuropathy, and deafness. My lab has shown that a mutation in TFG (p.R106C) causes a recessive form of HSP. To establish a tractable model for the study of this disease, I am using human iPSCs to determine the impact of the TFG p.R106C mutation on protein secretion and neuronal maintenance.

Human iPSCs can be derived from patient-specific somatic cells and can be directed to differentiate into all three germ layers of the human body. iPSCs are the ideal platform for extensively researching patient-specific diseases as well as *in vitro* testing of pharmaceuticals for these diseases. Although patient-derived iPSCs are often used to study the effects of genetic perturbations in culture, epigenetic effects can complicate or even confound the interpretation of results. Instead, I am taking advantage of a well-characterized iPSC line, and have used genome-editing approaches to create mutations in TFG that cause neurodegeneration. In this way, I was able to define the consequences of TFG mutations in a highly specific manner.

Grants Received:

NIH T32 Trainee; NIH Ruth L. Kirschstein National Research Service Award
NIH T32-HD041921 2015-2017.

Publications:

McMillan EL, Kamps AL, Lake SS, Svendsen CN, Bhattacharyya A, "Gene expression changes in the MAPK pathway in both Fragile C and Down syndrome human neural progenitor cells." American Journal of Stem Cells. June 2012.

Andres RH, Horie N, Slikker W, Keren-Gill H, Zhan K, Sun G, Manley NC, Pereira MP, Sheikh LA, **McMillan EL**, Schaar BT, Svendsen CN, Bliss TM, Steinberg GK. "Human neural stem cells enhance structural plasticity and axonal transport in the ischaemic brain." Brain. 2011 Jun; 134 (Pt 6): 1777-89.

Sareen D, **McMillan E**, Ebert AD, Shelley BC, Johnson JA, Meisner LF, Svendsen CN. "Chromosome 7 and 19 trisomy in cultured human neural progenitor cells." PLoS One. 2009 Oct 29;4 (10):e7630.

Bhattacharyya A, **McMillan E**, Chen SI, Wallace K and Svendsen CN. (2009) "A critical period in cortical interneuron neurogenesis in Down syndrome revealed by human neural progenitor cells" (Dev Neurosci; 31(6) : 497-510).

Meyer JS, Shearer RL, Capowski EE, Wright LS, Wallace KA, **McMillan EL**, Zhang SC, Gamm DM. "Modeling early retinal development with human embryonic and induced pluripotent stem cells." Proc Natl Acad Sci U S A. 2009 Sep 29;106(39):16698-703. Epub 2009 Aug 25.

Kim HJ, **McMillan E**, Han F, Svendsen CN. "Regionally specified human neural progenitor cells derived from the mesencephalon and forebrain undergo increased neurogenesis following overexpression of ASCL1." Stem Cells. 2009 Feb;27(2):390-8.

Ebert AD, **McMillan EL**, Svendsen CN. "Isolating, expanding, and infecting human and rodent fetal neural progenitor cells." Curr Protoc Stem Cell Biol. 2008 Sep;Chapter 2:Unit 2D.2.

Bhattacharyya A, **McMillan E**, Wallace K, Tubon TC Jr, Capowski EE, Svendsen CN. "Normal Neurogenesis but Abnormal Gene Expression in Human Fragile X Cortical Progenitor Cells." Stem Cells Dev. 2008 Feb;17(1):107-17.

Siwkowski AM, Madge LA, Koo S, **McMillan EL**, Monia BP, Pober JS, Baker BF. "Effects of antisense oligonucleotide-mediated depletion of tumor necrosis factor (TNF) receptor 1-associated death domain protein on TNF-induced gene expression." Mol Pharmacol. 2004 Sep;66(3):572-9.