

# The Role of the Integrated Stress Response in tRNA Synthetase-Associated Peripheral Neuropathies

## January 19

Tuesday, 12:30pm

Live Webinar  
via Zoom Conference



**Speaker: Robert W. Burgess, Ph.D.**  
Professor  
The Jackson Laboratory  
Bar Harbor, ME

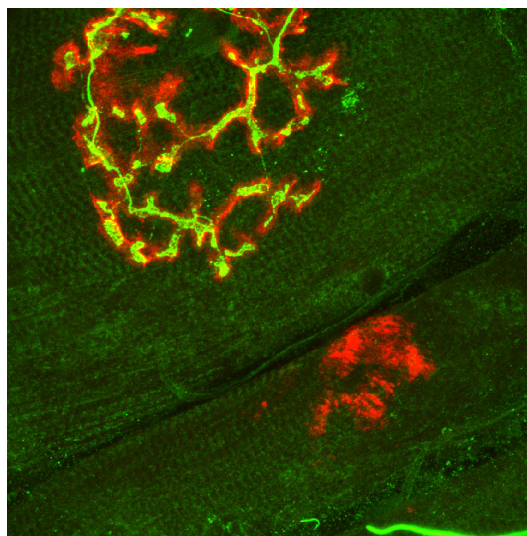
**Host: Dianna E. Willis, Ph.D.**

For more information,  
please contact  
**Darlene White**  
[daw9085@med.cornell.edu](mailto:daw9085@med.cornell.edu)

**Burke Neurological Institute**  
Academic Affiliate of Weill Cornell Medicine  
785 Mamaroneck Avenue  
White Plains, NY 10605  
[burke.weill.cornell.edu](http://burke.weill.cornell.edu)

## Abstract

Degeneration of peripheral motor and sensory axons is a hallmark of Charcot-Marie-Tooth disease (CMT), a family of inherited, length-dependent peripheral neuropathies. The largest gene family associated with CMT is the amino acyl tRNA synthetase gene family. These genes are ubiquitously expressed housekeeping genes that encode the enzymes that charge amino acids onto their cognate tRNAs for protein translation. Using mouse models of CMT, we have identified gene expression signatures consistent with activation of the integrated stress response. The stress response is activated selectively in a subset of motor and sensory neurons, and using both genetic and pharmacological tests, we have shown that it is activated through the sensor kinase GCN2. Importantly, blocking GCN2 activation not only eliminates the integrated stress response, it also greatly reduces the severity of the neuropathy. Therefore, our results indicate that chronic activation of the integrated stress response is contributing to the pathophysiology of tRNA synthetase-associated neuropathies, and that GCN2 is a viable therapeutic target for these disorders.



1. Spaulding, E. L., J. N. Sleight, K. H. Morelli, M. J. Pinter, R. W. Burgess et al., 2016 Synaptic Deficits at Neuromuscular Junctions in Two Mouse Models of Charcot-Marie-Tooth Type 2d. *J Neurosci* 36: 3254-3267.
2. Spaulding, E. L., and R. W. Burgess, 2017 Accumulating Evidence for Axonal Translation in Neuronal Homeostasis. *Front Neurosci* 11: 312
3. Morelli, K. H., L. B. Griffin, N. K. Pyne, L. M. Wallace, A. M. Fowler et al., 2019 Allele-specific RNA interference prevents neuropathy in Charcot-Marie-Tooth disease type 2D mouse models. *J Clin Invest* 129: 5568-5583.

