Specific Aims: The overarching question guiding Dr. Graves' research interest is *'how can symptom science be used to help explain, predict, and mange symptoms (also known as SHC's) following spinal cord injury?'* Dr. Graves is proposing two interdependent aims that will contribute to the larger work of the Bogie lab and generate preliminary data to support a CDA application.

Specific Aim 1: Conduct secondary analysis of existing whole blood and muscle tissue collected from the Bogie Labs prior studies to run epigenome wide analysis (EWAS) to discover genes presented differentially in the two tissue types. A prospective pilot study sampling newly enrolled participants in Dr. Bogie's Biomarkers for Early Identification of Pressure Injury Risk study (**RX003081**) will also collect blood-based outcome measures.

This ***hypothesis generating*** approach will provide the foundation for addressing future questions including:

1. Aging vs injury epigenomic changes that drive tissue decline.
2. Broader understanding the variation of epigenetic and phenotypic effects on pressure injury risk.

Specific Aim 2: Conduct a retrospective secondary analysis on the SCI-PIR database developed by the Bogie Lab [14,15] Machine learning methods will be applied to extract and identify common symptoms and/or risk factors post SCI. "cluster" classifications of symptoms/SHCs after SCI will be developed including for those with and without a history of pressure injuries. This aim will lay the groundwork toward developing a multi-symptom inventory assessment specific Veterans living with SCI.

Hypothesis: In addition to genetic risk factors, there are common symptoms and/or environmental determinants of pressure injury risk that co-occur and support the identification of latent classes of symptomsin individuals after spinal cord injury.

Methodology/Analysis plan: Outcome measures will be collected using PROMIS® (patient reported outcomes measurement information system), and the *Neuro-Qol*™ short form. Development and psychometric evaluation of an SCI multi-symptom inventory with variables measured including but not limited to, adult domains of anxiety, bowel function, cognitive function, depression, fatigue, sleep disturbance, pressure injury, urinary bladder function, upper extremity function. This has the potential to provide a standardized approach to symptom/SHC data collection across studies in this research area.

Proposed analysis methods include latent class analysis, classification and regression trees (CHART; machine learning methods) and generalized mixed modeling. Dr. Graves will work closely with Drs. Sun and Chan (see ***Mentoring Plan*** below) to run advanced modeling. This will include additional training on specific software as needed. Power estimation will be conducted to determine the appropriate sample size for EWAS analysis.

Use of Illumina 450K array, to detect genome wide methylation in whole blood samples obtained by the Bogie Lab. The array measures methylation and unmethylated signals at >485K single CpG sites. Analysis will be carried out by the Genomics Core facility at Case Western Reserve University.