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Mentor: Dr. Gregory Funk

I am originally from Southern Ontario and completed a Bachelor of Science majoring in Human Kinetics at the University of Guelph. Since the first year of my undergraduate degree, my career goal has been to direct my own independent research program. During this degree, I was fortunate to work in a number of different labs, helping me to determine my scientific interests. I worked on projects spanning equine hoof morphology, my first independent research project (Dr. JJ Thomason), to protein folding structure (RY Yada and JR Dutcher) as a NSERC summer studentship, to human gait biomechanics as my fourth year honours thesis (JP Dickey).

Based on these experiences, I realized I was most interested in understanding how neurons that drive muscles, i.e. motoneurons, are recruited and activated by the brain to generate movement. I sought out Dr. Andrew Fuglevand as a PhD mentor at the University of Arizona, where I evaluated the potential roles of motoneuron cellular (membrane) properties in controlling motoneuron activity during volitional behaviours in humans. It is a challenge to infer mechanisms in an intact system, but through careful experimental design, coupled with computer modeling, I was able to explore these questions indirectly.

Through this research, I became increasingly interested in understanding the cellular and synaptic mechanisms controlling motoneuron recruitment and activation. Clearly, such questions cannot be addressed directly in humans so in my postdoctoral fellowship I moved to Dr. Funk's lab to study in animal models how intrinsic, synaptic and modulatory properties control motoneuron activity during the relatively "simple" behaviour of breathing. The breathing circuit is an excellent model to investigate how microcircuits configure to produce behaviour, which also has translational potential.

Obstructive sleep apnea is a debilitating sleep disorder affecting more than ten percent of people. During sleep, patients who suffer from obstructive sleep apnea stop breathing many times a night because upper airway muscles, including most importantly the tongue, collapse and block the airway. Therefore, those afflicted never get a good night's sleep and are susceptible to an increased risk of motor vehicle and workplace accidents due to always feeling sleepy. Furthermore, they develop other conditions including high blood pressure, heart attacks, angina (chest pain), and stroke. The main therapy that currently exists, CPAP (continuous positive airway pressure) is effective, but user compliance is low because the mask they have to wear is often cumbersome and may be uncomfortable, and the machine is loud. Therefore, novel therapies are needed.

To address this need, we have begun to study a critical population of neurons involved in transmitting breathing impulses to the muscles of the tongue that are necessary for keeping the airway open. The tongue is controlled by a basic 3-

part motor network involving (1) the preBötzinger Complex (preBötC) that generates rhythmic breathing, (2) hypoglossal premotoneurons that transmit rhythmic inspiratory drive from the preBötC to (3) hypoglossal motoneurons that activate the genioglossus muscle of the tongue, which prevents the tongue from blocking the airway during inspiration. During sleep, preBötC activity changes very little; reductions in the excitability of inspiratory premotoneurons and motoneurons are primarily responsible for reduced airway tone, and apnea, during sleep. Of the hypoglossal premotoneurons and motoneurons, only the latter have been studied in any detail. The field widely recognizes the need for greater understanding of hypoglossal premotoneurons. The problem has been that, in contrast to hypoglossal motoneurons, which are easy to study and among the best characterized neurons in the brain, hypoglossal premotoneurons are extremely difficult to find. They are dispersed at low density over a wide area in the brain and intermingled with many other types of neurons.

In the manuscript published in eLife, we have taken a developmental genetics approach to overcome this problem; we have identified, labeled and begun to characterize at least one source of XII inspiratory premotoneurons. Our discovery of the origins of this important neural population is the necessary first step in determining whether this population of neurons might be useful as a novel therapy target for drug development for sleep apnea.