Abstract of proposed student project (1 page limit. This should mirror the aims page of a grant and CLEARLY indicate the student's role.)

Patients with **spinal cord injury** (**SCI**) frequently develop lower urinary dysfunction. The resultant bladder overfilling causes life-threatening kidney damage or incontinence, and restoring bladder function is often ranked as a patient's most desired area of therapeutic improvement[1]. Current therapeutics are often ineffective and have undesirable side effects.

Ampakines are allosteric modulators of AMPA receptor channel kinetics that enhance glutamatergic synaptic transmission[2,3]. Ampakines have been tested in clinical trials related to learning and memory with no adverse effects reported[4,5]. Co-I Dr. Fuller's group has recently established that ampakine treatment can enhance breathing after SCI[6,7]. That work in a "preclinical" rodent model has shown that low dose ampakine therapy is safe after SCI and can have a beneficial impact on the ability to breathe. Here we propose to determine if ampakine treatment can restore bladder function after SCI.

Our rationale for studying ampakines and bladder function is based on the fact that glutamate and AMPA receptors are important signaling factors in neural pathways of the voiding reflex. This includes both the descending control of motor outputs and afferent signaling inputs. Further, glutamatergic neurotransmission is impacted after SCI and likely contributes to impaired neural control of the bladder[8–14]. Therefore, our **central hypothesis is that systemic delivery of ampakines can restore bladder function following thoracic spinal contusion by amplifying descending micturition circuits.** This hypothesis is supported by stunning results in a few preliminary experiments. In a rat model of SCI that mimics what happens in human spinal injury, we observed that acute doses of ampakine CX1739 could almost immediately restore contractions in a previously areflexive bladder. Further, the ampakine treatment normalized voided volume and contraction intervals to near non-injured controls. These findings are fascinating as no current treatments can enhance bladder circuits following SCI.

Assess the effects of chronic low-dose ampakine on recovery of bladder function and protection from neuronal death following SCI. This aim will evaluate the therapeutic effect of ampakine intervention on the recovery of bladder function after chronic (i.e., "long term") SCI. We hypothesize that ampakines can enhance the function and the survival of spinal cord neurons, resulting in a reduction of the chronic bladder deficits related to SCI. Preliminary studies from Dr. Fuller's group in rats suggest that ampakines can attenuate spinal cord neuronal loss after injury. We expect similar results and that low-dose ampakine will enhance and shorten the duration of recovery of bladder function following SCI. These data will be essential for extramural funding applications to demonstrate chronic efficacy.

Hypothesis: Chronic low-dose ampakine can enhance the recovery of bladder function and provide a neuroprotective effect following SCI.

Objective 1. Evaluate the effects of chronic low-dose ampakine on bladder function following SCI. This objective aims to evaluate the effects of daily administration of ampakine CX1739 or vehicle at the onset of injury on bladder health. Weekly we will test voiding behaviors using metabolic cages (24-hour testing period). We will use urine analysis strips to evaluate the collected urine for disease biomarkers, including protein, leukocytes, ketones, and pH. We will perform terminal cystometric experiments at 10-weeks for more detailed urodynamic testing and evaluation of external urethral sphincter coordination with detrusor contractions. Additionally, we will collect bladders to evaluate bladder weight, wall thickness, collagen deposition, and inflammatory markers of bladder dysfunction (**Figure 1**).

The **FSVP student** on this project will assist with objective 2 experiments in a cohort of 10-12 rats. They will assist with the surgical model of injury, care for the rats following injury, injection of daily ampakine, recording metabolic cage activity, locomotor testing, and assist postdoc Firoj Alom with terminal cytometric studies , and collection of tissue.