Biomarkers of kynurenine pathway modulator AV-101: first steps to treating suicidal Veterans

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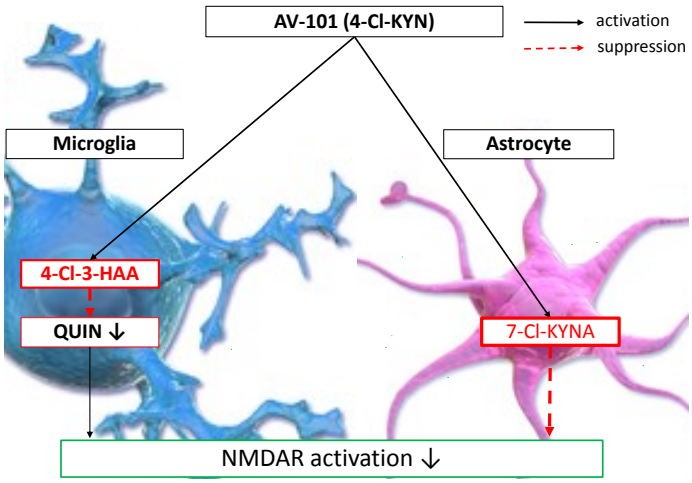
Background: Suicide is the 10th leading cause of death in the U.S.[1], and is 2-7 times higher in Veterans than age- and sex-matched civilians[2]. Standard psychiatric medications (such as lithium) are anti-suicidal with prolonged use only, and do not impact acute suicidality. A priority for suicide prevention is to define novel treatment targets for safe and rapidly-acting interventions. Recent studies have associated suicide and medically severe suicide attempt (MSSA) with dysregulation of the brain kynurenine pathway (KP). KP dysregulation manifests as high levels of neurotoxic quinolinic acid (QUIN), a glutamate receptor (NMDAR) agonist, relative to picolinic acid (PIC), a QUIN antagonist, and low neuroprotective kynurenic acid (KYNA), an NMDAR glycine B site antagonist[3]. High QUIN/PIC or low KYNA predispose to excessive NMDAR activation, a molecular target purportedly involved in rapid improvement of suicidality with agents such as ketamine[4]. AV-101 (4-chlorokynurenine, 4-Cl-KYN) is an oral pro-drug that could reverse KP dysregulation with downstream NMDAR deactivation. AV-101 stimulates astrocyte-produced 7-chlorokynurenic acid (7-Cl-KYNA), a potent NMDAR glycine B site antagonist[5], and microglia-produced 4-chloro-3-hydroxyanthanillic acid (4-Cl-3-HAA), an indirect QUIN inhibitor[6] (see Figure). Phase-1 testing showed that AV-101 is safe for use in humans, and is metabolized to 7-Cl-KYN in 1.5 to 2 hours after intake.



Objective: Before testing possible anti-suicidal properties, biomarkers need to be defined to show that AV-101 engages the NMDAR which is thought to underlie rapid improvement in suicidality. The objective of the current study is to define valid and sensitive neurophysiological markers with a dose-response relationship with AV-101 as evidence of NMDAR engagement, as well as study safety and tolerability. Outcomes will provide pivotal data for competitive grant proposals focused on effects of AV-101, and KP and NMDAR modulation on moderate to severe suicidal ideation or behaviors in active duty military personnel or Veterans.

Methods: We will recruit 12 healthy and non-psychiatrically ill OEF/OIF/OND Veterans (age 25-64) who will receive two single doses of AV-101 (720 mg, 1440 mg) and placebo in a randomized, double-blind, crossover design with one week wash-out between conditions. Neurophysiological measures collected at baseline (pre-treatment) and hourly for 5 hours following medication intake are resting state EEG, Mismatch Negativity amplitude, and P50 sensory gating, measures sensitive to modulation of different NMDAR mechanisms. Subjects will be recruited using our infrastructure that we use to successfully recruit Veterans with mood- or anxiety disorders. Medication and placebo will be provided to us by courtesy of VistaGen Therapeutics (per Mark Smith, MD, VistaGen Chief Medical Officer). Repeated measures General Linear Models will be used to test dose-response relationships. PI Dr. Lijffijt, Ph.D., and a senior research coordinator will screen subjects and conduct research procedures. Dr. Lijffijt will perform neurophysiology and statistical analyses. Drs. Swann and Mathew will monitor subject safety.

References: [1]LCWK1 (2016), www.cdc.gov/nchs/nvss/mortality/lcwk1.htm; [2]USDVA (2016), Suicide among veterans and other Americans 2001-2014, Office of Suicide Prevention; [3]Bryleva, Brundin (2017), Curr Top Behav Neurosci 31:269-84; [4]Price, Mathew (2015), CNS Drugs 26:181-8; [5]Hokari et al (1996), Neuroreport 20:15-8; [6]Yates et al. (2006), J Neurotrauma 23:866-81.