Effect of Positive Allosteric modulation of Dopamine D2 Receptors on Respiration in Mouse models of Rett Syndrome

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Scientific Abstract:

Disturbances in respiration characterized by frequent apneas, periodic breathing and an irregular breath to breath interval affects the majority of individuals with Rett syndrome (RTT). A significant contributor to these disturbances is excess activity of post-inspiratory (post-I) and late expiratory neurons. Recordings from central vagus, hypoglossal and abdominal nerves show augmented and prolonged activity during apnea. Post-I and late expiratory neurons are inhibited by serotonin 1A agonists and dopamine D2 agonists. Sarizotan, a 5-HT_{1a} and D2 like agonist, is effective in reducing the incidence of apnea and restoring regularity in *Mecp2*$^{Bird/+}$ and *Mecp2*$^{R168X/+}$ mice. Sarizotan is currently in a clinical trial with RTT patients age 4 and older. Sarizotan was originally tested as therapy in Parkinson's disease. Compounds are now being developed to effect positive allosteric modulation (PAM) of D2 receptors with a view of using them in Parkinson's disease. The specific aims of this proposal are to show that 5-fluoro-4- (hydroxymethyl)-2-methoxyphenyl]-(4-fluoro-1H-indol-1-yl) methanone (UCB Compound), a D2 PAM, enhances dopamine responses in expiratory neurons of wild type, *Mecp2*$^{Bird/+}$ and *Mecp2*$^{R168X/+}$ mice. In separate studies the acute effects of the PAM on respiration in awake mice will be examined. The acute effects will enable us to determine the dose for long term studies in mice. A crossover design will be used to study the effects of the PAM when given for one month to wild type and *Mecp2*$^{Bird/+}$ and *Mecp2*$^{R168X/+}$ mice. Respiration and locomotion will be measured during the treatment and placebo periods. In addition since Mecp2 deficient mice have a blunted respiratory response to CO_2 we will examine CO_2 response before and after acute and long term administration of UCB Compound.