**Paper title: Chronic prenatal interleukin-17 is sufficient to cause sex-specific ASD-phenotypes in a mouse model**

**Introduction**

Pro-inflammatory maternal immune activation (MIA) during gestation has been associated with autism spectrum disorder (ASD) in clinical populations (1, 2), with some further suggesting that maternal immunological perturbations may serve a direct, causal role in its pathogenesis (3, 4). Specifically, studies in both humans and animal models have implicated elevated *maternal* interleukin-17 (IL-17), a key pro-inflammatory cytokine, in offspring ASD and ASD-related phenotypes (5). The dysregulation of both T helper 17 (Th17) lymphocytes, a subpopulation of CD4 + T cells that secrete IL-17 family cytokines, and elevated levels of IL-17A have also been linked directly to ASD *within individuals* (6, 7), as have copy-number variants in the *IL17* gene (8). One cross-sectional study reported that nearly 50% of children with ASD (and nearly 70% with severe ASD) had above-average levels of serum IL-17a (9). Interestingly, serum levels of IL-17 have also been shown to be increased in children with ASD who experienced symptomatic regression compared to those who did not regress (10).

In animals, behavioral phenotypes thought to model dimensions of ASD have previously been shown to be sensitive to broad prenatal immune insult (11-13). More specifically, research has implicated IL-17A signaling as necessary for the effects of gestational poly(I:C), a viral mimetic and MIA model, on mouse offspring ASD-like phenotypes. Choi et al. (2016) demonstrated that the selective inhibition of IL-17-producing Th17 cells by genetic deletion of a transcription factor critical to their development (RORyt), or maternal pre-treatment with IL-17a blocking antibody, resulted in a rescue of MIA-associated ASD-like behaviors, including social and repetitive/stereotyped behaviors, as well as cortical disorganization (14). Cortical “patches” or disorganized regions of cortex have also been implicated in human ASD (15). Subsequent work by the same group further revealed that these phenotypes may be due to hyperactivity of pyramidal neurons and decreased GABAergic drive in the primary somatosensory cortex (16). Critically, this work reveals that maternal mechanisms, mediated by IL-17, may underlie ASD-like effects in MIA offspring.

IL-17 can act both via maternal systems to influence neurodevelopment, but also directly on neurons themselves. For instance, IL-17 mechanisms can alter cell differentiation, survival, and signaling (5). Liu et al. (2014) demonstrated that IL-17a regulates adult hippocampal neurogenesis, the levels of other pro- and anti-inflammatory cytokines in the hippocampal dentate gyrus, and hippocampal electrophysiology, such that IL-17a knockout animals exhibit increased dentate synaptic excitability and hippocampal neurogenesis (17).

While it has been shown that IL-17 pathways mediate and are necessary for the effects of MIA on offspring neurodevelopment and behavior, no studies have yet examined whether chronic, maternal IL-17 throughout pregnancy is in fact sufficient to induce these effects. To better understand the neurodevelopmental programming role of this specific inflammatory factor, we exposed dams to IL-17 continuously throughout gestation. Using a combination of behavioral, genetic, and histological approaches, we found that embryonic cortical morphogenesis and cortical transcriptomic profiles, as well as adult neurobiology and behavior, in male offspring are altered by prenatal maternal IL-17. This work underscores the causal role of maternal IL-17 in the generation of ASD-relevant phenotypes in offspring.