# THE HARTWELL FOUNDATION

## 2015 Individual Biomedical Research Award

**John Lukens, Ph.D.**

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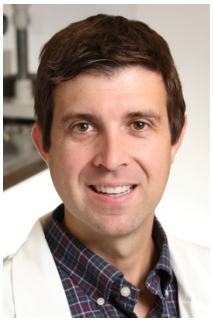
**University of Virginia**



### Targeting the Interplay between the Immune System and Microbiota in Autism Spectrum Disorder

Autism spectrum disorder (ASD) has emerged as one of the most prevalent and pressing pediatric disorders in the U.S. It is estimated that 1 in 68 American children will develop ASD; but the incidence is expected to continue increasing at an unprecedented rate if preventative measures are not soon identified. Unfortunately, treatment options that target the root causes of ASD do not exist. Initial speculation suggested a key role for genetic mutations; however, it is now known that almost 80% of all ASD cannot be explained by genetic factors alone. This has prompted many to speculate that a diverse array of evolving environmental, socioeconomic and individual behavioral considerations may be to blame, including maternal obesity, infection during pregnancy, changes in dietary consumption, and pollutants known to provoke hyperactive immune responses. These conditions may contribute indirectly to dysregulated immune responses by altering the bacterial communities in the gut microbiome (microbiota), which can make the body generate an immune reaction against its own intestinal tissue. In support of this view, John recently demonstrated in a mouse how dietary modulation of the microbiome affects autoinflammatory disease, where aberrant regulation of the microbiome (dysbiosis) appeared to elevate systemic levels of the inflammatory mediator interleukin-1 (IL-1). He theorizes that IL-1 signaling may be the critical link between the microbiome and ASD; providing a means for reciprocal cross-regulation of IL-1 expression and microbiota diversity. To test his working hypothesis, he will identify the molecular components of elevated IL-1 signaling that contribute to dysregulated inflammatory responses and neurodevelopmental abnormalities in established mouse models of maternal immune activated (MIA) autism and Rett syndrome, a genetic mutation that causes severe progressive impairment of growth and development of the brain. He will determine whether aberrant IL-1 production contributes to disease progression by genetically ablating key mediators of IL-1 signaling and production. He will also determine the therapeutic potential of targeting IL-1 signaling to regulate microbiome-mediated autism. If John is successful, it will be possible to ascertain whether the dysbiosis associated with neurodevelopmental disorders in ASD is a cause or consequence of dysregulated IL-1 production, potentially providing a unifying explanation for the diverse epidemiological evidence associated with the disorder. The identification of target drug therapies will provide an opportunity for clinical translation, which will focus effort to develop the first ever approach to treat, prevent or possibly even reverse ASD.