THE HARTWELL FOUNDATION

2016 Individual Biomedical Research Award

Debra Silver, Ph.D.

Assistant Professor
Department of Molecular Genetics and Microbiology

Duke University

Amelioration of Neural Stem Cell Defects Underlying Zika Virus-Induced Microcephaly

Zika virus (ZIKV) is a mosquito-borne infective pathogen that when encountered during pregnancy may cause a neurodevelopmental birth defect, often associated with a significantly smaller brain (microcephaly). Babies borne from infected mothers endure cognitive deficiencies, vision and hearing deficits, impaired growth, reduced quality of life and a shorter life span. There is also a strong link between the virus infection and the appearance of Guillain-Barré syndrome (GBS), an unusual autoimmune disorder that affects the nervous system as acute weakness or paralysis in the arms and legs, and in severe cases difficulty breathing. In the United States ZIKV is an emerging health crisis with confirmed diagnosis in all 50 states. The CDC confirms about 1300 pregnant women are infected ZIKV in the U.S., with nearly triple that figure across all U.S. Territories; but the numbers are predicted to rapidly increase. Unfortunately, an effective ZIKV vaccine does not exist and will take at least 3 years to develop. To address the health effects and risks associated with ZIKV there is an urgent need to understand how the virus infection causes microcephaly and contributes to GBS. For example, although ZIKV has been shown to infect neural precursor cells (stem cells), it is unknown whether the infection directly triggers microcephaly or whether viral exposure during pregnancy has the most deleterious impact. There remain many gaps in our understanding of ZIKV and many perplexing questions exist. With so little known about the virus it is also of concern that prenatal ZIKV exposure could disrupt brain development in other, more subtle ways that would not manifest as neonatal microcephaly. For example, alterations in neural stem cell function could increase the appearance of aberrant types of neurons, a feature often associated with schizophrenia. Similarly, activation of the autoimmune system associated with GBS following ZIKV infection resonates with maternal autoantibody related autism. To address how ZIKV infection disrupts typical brain development, Debra proposes to utilize complementary approaches in tissue culture and mouse models to better define ZIKV infection and its impact at distinct stages of fetus development. Her approach will provide the opportunity to discover the mechanism of action of ZIKV on neural stem cells, identify new targets for therapeutic intervention and enable the identification of anti-viral compounds to ameliorate the impact of ZIKV on fetal brain development. If Debra is successful, she will resolve the mechanism that governs ZIKV-induced alterations in fetal brain development, which will inform translation to novel drug therapies that will not only benefit all children at risk for ZIKV, but may also strategically impact the course of medical research directed at understanding GBS, schizophrenia and autism.