THE HARTWELL FOUNDATION

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Defining How an Emerging Polio-like Virus Causes Neurological Complications

Acute flaccid myelitis (AFM) is a rare but serious condition of young children that affects the nervous system with onset symptoms of limb weakness and paralysis that disturbingly, resemble polio. Sometimes AFM can weaken the muscles needed for breathing, which can lead to respiratory failure. The first reported outbreak in the U.S. occurred in 2012. With about 600 documented cases from 2014 through 2018, almost all pediatric AFM cases required hospitalization, with more than half being admitted into intensive care. By contrast, it is estimated a million children have endured a mild form of the illness that did not require medical attention. More than 90% of patients with AFM have experienced a mild respiratory illness or fever consistent with a viral infection before they developed AFM and of those tested all were negative for polio. Seasonality of AFM incidence (every two years) suggests a viral etiology and although the definitive cause of AFM infection remains unconfirmed, enterovirus D68 (EV-D68) is strongly suspected based on the temporal-geographic association between polio and D68 infections. Currently, there are no treatments to cure AFM; no way to know which children will have life-altering long-term neurological damage; no explanation why a small number of affected children do not recover; and no way to stop the damage once it has occurred. Moreover, it is unknown if viral or host determinants have enabled EV-D68 to emerge and cause AFM. To address these challenges, Rob proposes to define the combination of host and/or viral genes that will enable enterovirus D68 to grow in neurons. Using induced pluripotent stem cells (iPSC) derived from patients who developed AFM, he will use an unbiased genome-wide screen (CRISPR/Cas9 gene editing) to identify essential host factors for neuronal infection by EV-D68. Effectively, iPSC will be differentiated into a library of motor neurons with distinct genetic mutations and then subsequently tested for their susceptibility to EV-D68 infection. The neurons infected with EV-D68 that have mutations in host pathways required for viral replication will survive and the mutations will be identifiable by sequencing the guide RNA. Viral production and neuronal death will be monitored, as an increase in viral production within neurons may lead to a robust, localized response and subsequent loss of neuronal function, whereas an increase in neuronal cell death absent an increase in viral production may signal particular neuronal sensitivity. RNA-Sequencing and whole exome sequencing will be used to determine if host transcriptional responses and genetic differences are correlated with the observed phenotypes. If successful, identification of essential host factors will provide new therapeutic targets and a pathway for developing biomarkers with predictive value for determining which children will be at risk for developing neurological complications from this emerging viral threat that currently has no treatment.