# THE HARTWELL FOUNDATION

## 2017 Individual Biomedical Research Award

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### Rescuing the Expression of Healthy Genes from the Dormant X Chromosome in Neurodevelopmental Disorders

Neurodevelopmental disorders (NDD) are a group of neuropsychiatric conditions caused by alteration of brain function during childhood growth and development, often presenting with impaired motor function and affecting to a variable extent self-control, emotions, learning ability, and memory. With a high prevalence in boys, NDD affect almost 4.6 million children in United States. Many affected children have more than one condition, including cerebral palsy, intellectual disability, autism, attention-deficit/hyperactivity disorder, conduct disorder, as well as certain impairments in vision and hearing. The complex interplay of genetics and the environment are known to be important in NDD, which are unfortunately life-long conditions with no available cure and only management of symptoms. Gender is an important factor, but surprisingly little is known about the neurologic profile in girls, where certain autism syndromes like Rett occur exclusively in females. In this regard, the majority of NDD have multiple genomic alterations, with mutations known to occur among more than 100 protein-coding genes located on the X chromosome. To be clear, in humans one functional chromosome is inherited from each parent: a pair of X and Y chromosome determine a male and a pair of X chromosomes determines a female. During early embryonic development in females, one of the two X chromosomes is randomly and permanently inactivated in all cells other than egg cells, which effectively equalizes expression of X-linked gene products between XX females and XY males. Thus in females, even though dysfunctional genes on the active X chromosome are the cause of NDD, each defective cell holds a possible key to a cure if the silenced chromosome can be reactivated. To address this prospect, Sanchita proposes a new therapeutic strategy to compensate for X-linked gene deficiencies in young girls affected with NDD that will boost the expression of healthy genes from their dormant X chromosome and reverse the behavioral deficits. Her approach is based upon her discoveries about X chromosome inactivation factors that regulate cell signaling and transcription; and how such factors, even in late stages of growth and development, can be controlled to reactivate the X-linked genes without detrimental effects on cell survival or proliferation. On this basis Sanchita will seek to evaluate lead drug compounds for reactivation in both a preclinical neuron cell model derived from a female patient with Fragile X syndrome and in a mouse model of Rett syndrome. If Sanchita is successful in identifying safe and effective drug candidates, it will lay a foundation for subsequent clinical trials and the latent potential to establish a cure. Effectively and efficiently compensating for X-linked gene deficiencies in young girls with NDD would bring immeasurable relief to affected children and their families.