

THE HARTWELL FOUNDATION

2007 Individual Biomedical Research Award

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Discovery of Common Synaptic Mechanisms in Novel Mouse Models of Autism

"We deal with special needs every day and I try to not let it define my family" is a compelling statement often made by families in their emotional struggle to deal with children affected by autism. Substantially impaired social interaction skills, verbal and nonverbal communication problems, and unusual repetitive or severely limited activities and interests characterize the disorder. By contrast, autism is also occasionally, associated with remarkable memory capacity or skills (savant behavior). A spectrum of related disorders includes Asperger syndrome, Rett syndrome, childhood disintegrative disorder, and pervasive developmental disorder. Numerous similarities exist between autism and schizophrenia, as well as other learning disabilities, like attention deficit/attention deficit hyperactivity disorder and obsessive-compulsive disorder. It has even been suggested there may be a possible connection between autism and immune-mediated diseases with neuro-immune or neuro-autoimmune dysfunction, including Alzheimer disease, ALS, chronic fatigue syndrome, fibromyalgia, and MS. While early diagnosis with vigorous intervention can lead to significantly improved outcomes for children with autism, there are no effective drug therapies. Recently, Dr. Powell published the first mouse model of autism, based upon one variation in the human disorder, a single point mutation (R451C knockin) of a conserved residue present in neuroligin-3. The mice had impaired social behavior but enhanced (savant-like) spatial learning abilities. The mice also displayed an increase in inhibitory synaptic transmission, but no change in excitatory synapses, suggesting that antagonists of inhibitory synaptic transmission might be a useful target for behavioral abnormalities. Powell proposes mouse model mutations in neuroligin-3 binding partners, neurexin-1 and shank3, which represent other genetic causes of autism. If successful, he intends to identify a common abnormality among the three models of autism, which will perhaps provide a drug target for the first rational therapy for this devastating disease, providing relief for millions of affected children and their families.