THE HARTWELL FOUNDATION

2006 Individual Biomedical Research Award
2008 Biomedical Research Collaboration Award

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Unraveling Brain Circuitry Defects in Obsessive-Compulsive Disorders

Obsessive-compulsive disorder (OCD) is an incapacitating mental disease characterized by persistent intrusive thoughts or images (obsessions) and increasing anxiety, leading to uncontrollable repetitive or ritualistic actions (compulsions). It is a common pediatric mental illness, affecting about 2% of all children above age three. OCD has a major negative impact on the quality of life of affected children, including their self-esteem, education, social functioning and potential for future employment. No effective treatment is available to treat OCD. However, recent studies by Dr. Feng in mice have revealed a potential novel molecular mechanism for this disorder, where genetic deletion of the SAPAP3 gene leads to OCD-like behaviors. This SAPAP3 mutant mouse is the first known OCD animal model generated by a gene mutation. The mouse lacks a specific protein normally present at the excitatory synapses by which neurons communicate with one another in the brain, suggesting that defects in neuronal connections might play a critical role in the course of the disease. Using other genetic manipulations in this mouse model, Feng will seek to examine how mutation of the SAPAP3 gene contributes to defective signaling pathways and alteration in specific brain circuitry. If successful, his results will significantly advance understanding of the neuropathology of OCD and provide a unique basis for developing molecular target drug intervention in this disorder. Additional studies will be required to determine whether mutations in either the SAPAP3 gene or other genes important for synaptic function in the brain are associated with OCD in humans.

Dr. Feng also shares a Hartwell Collaboration Award with Andrew Pieper, MD, Ph.D., from UT Southwestern for “Rapid Discovery of Small Molecules for Drug Development in an Animal Model of Obsessive-Compulsive Disorder.” Their collaborative approach is designed to identify new compounds for OCD drug development that are both pharmacologically active and non-toxic in living animals, quickly elevating promising candidates to a very early stage of discovery.