

THE HARTWELL FOUNDATION

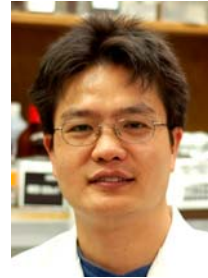
2006 Individual Biomedical Research Award

Guosheng Liang, Ph.D.

**Assistant Professor
Department of Molecular Genetics**

University of Texas Southwestern Medical Center

**Insig-mediated Regulation of Cholesterol Metabolism in
Cleft Palate**



Dr. Liang offers an exciting hypothesis regarding the cause of cleft palate, which tragically affects 1:600 births in the US every year. Individuals so affected have difficulty with feeding, speech, hearing and psychological development; and often, require long-term complex and painful treatments involving surgical, nutritional, dental, speech and behavioral interventions. The lack of knowledge regarding the molecular and pathological processes underlying these defects has hindered our ability to prevent these birth defects. In Sept 2006, Liang published data from his lab that revealed for the first time that the buildup of cholesterol precursors is a key factor in causing facial malformation. By feeding pregnant female mice lovastatin, a generic inhibitor of cholesterol synthesis that lowers the levels of LDL cholesterol and triglyceride levels while raising HDL cholesterol (the "good" cholesterol), Dr. Liang was able to prevent facial defects *in utero*. He proposes that the altered regulation of cholesterol biosynthesis (e.g., build-up of a toxic cholesterol precursor or precursors) interferes with normal craniofacial development. His hypothesis is supported by a report (Palo Alto, 2007) that mouse embryos lacking the GSK-3 β gene exhibit cleft palate and midline defects, which is relevant because cholesterol accumulation occurs with inhibition of GSK-3 β activity. The Liang hypothesis is now the dramatic center of possibilities in the cause of cleft palate. If his hypothesis is correct, the results of this innovative research will provide an opportunity for design of specific inhibitors targeting the cholesterol synthesis pathway, hopefully with ultimate translation to the prenatal patient population at risk.