THE HARTWELL FOUNDATION

2012 Individual Biomedical Research Award

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Novel Strategies for Fetal Protection During Antiphospholipid Syndrome

Approximately 240,000 US births each year are complicated by the maternal autoimmune disease known as antiphospholipid syndrome (APS). In APS, the immune system mistakenly identifies certain cell membrane constituents (phospholipids and proteins) as foreign substances and generates antibodies against them. These APS antibodies cause blood clotting (thrombosis), and adverse pregnancy outcomes including fetal death, fetal growth restriction, and life threatening maternal hypertension that often necessitates premature delivery. Annually approximately 80,000 US children are born prematurely or exhibit fetal growth restriction due to maternal APS. These children are at risk of early life-threatening disorders and major long-term neurologic impairment and chronic lung disease. Unfortunately, why mother and fetus are placed in danger by APS is poorly understood, and current therapies, which do not target the cause of the disease, lack efficacy. In 2011, Phil reported how the thrombosis associated with APS is initiated by APS antibody recognition of the protein β2GPI on cells lining blood vessels (endothelial cells). He observed that following antibody binding, subsequent biochemical events include a critical protein-protein interaction between β2GPI and the membrane receptor apoER2. Recently, along with collaborators he identified a novel monoclonal antibody that blocks APS antibody binding to β2GPI, and also a protein fragment (peptide) that blocks β2GPI-apoER2 interaction. In recent cell culture studies he also discovered that through apoER2-mediated processes, APS antibodies impaired the growth and migration of trophoblasts, which are placental cells critically important to the establishment of nutrient exchange between the mother and fetus. Whereas APS antibody administration to normal pregnant mice caused fetal death and growth restriction, pregnancies in mice globally lacking apoER2 were unaffected by the APS antibodies. Phil proposes to determine how APS causes fetal injury by delineating the role of trophoblast apoER2 in genetically-engineered mice, *in vivo*. He will address the unmet need for an effective therapy by determining in pregnant mice if the blocking antibody or blocking peptide protects the fetus from APS. If the mouse experiments are successful, paradigm-shifting clinical trials in human APS will soon follow and perhaps the life-threatening antiphospholipid syndrome for newborn infants can finally be eradicated.