THE HARTWELL FOUNDATION

2012 Individual Biomedical Research Award

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Prenatal Treatment of Hypoplastic Congenital Heart Defects by Modulation of Calcium Signaling During Development

Hypoplastic left heart syndrome is a devastating birth defect due to poor development of the left ventricle of the heart and accounts for 25% of all deaths from congenital heart disease. Infants with HLHS have a small, non-functional left ventricle that is unable to pump blood to the body. Multiple post natal surgeries are necessary for survival and without treatment the syndrome is fatal. Even following corrective surgery, HLHS carries a 5-year mortality of 20- 40% and renders affected children with significant physical and neurocognitive limitations. Given these sobering outcomes, many parents choose to terminate pregnancy or withdraw care once HLHS is diagnosed. While frequent use in the United States of prenatal screening by ultrasound allows HLHS to be diagnosed *in utero* before the heart has finished developing, it also provides a rare opportunity to intervene and restore ventricular growth prior to birth. Currently however, there are no established interventions for the prenatal treatment of HLHS. To address this unmet need, Mary acquired preliminary data using a zebrafish animal model to support an hypothesis that if calcium signaling in fundamental growth pathways of ventricular cardiomyocytes (heart tissue cells) is activated, ventricular hypertrophy (enlargement) will occur during fetal development *in utero*. She was also able to demonstrate surprisingly, that blood flow was not required for proper chamber formation or growth of ventricular cardiomyocytes, which is in opposition to the widely held paradigm that an alteration in blood flow within the heart is the cause of the anomaly. While the zebrafish provides a convenient model for specific gene disruptions in combination with tissue-specific and inducible expression systems, the inherent limitation in the zebrafish model is it has a two chamber heart compared to the four chambers of the human heart. Mary proposes to extend her unpublished observations on controlling ventricular growth in her zebrafish model system by establishing whether modulating calcium signaling (Ca^{2+}) in the four chambered heart of mouse embryos during their fetal development *in utero* can overcome the underdeveloped ventricle. In combination with human gene expression analysis she will also seek to identify calcium signaling pathway genes in pediatric heart tissue that are differentially expressed in children with congenital hypoplastic left heart disease. If her hypothesis is correct and Mary is successful an entirely new strategy for the prevention of HLHS will be possible, which will improve the survival and quality of life of affected children.