

THE HARTWELL FOUNDATION

2011 Individual Biomedical Research Award

Review of Proposed Research

Investigator: Jonathan E. Sears, M.D.
Associate Professor
Departments of Ophthalmology and Cell
Biology

Institution: Case Western Reserve University

Proposal: Preventing Retinopathy of Prematurity



In the womb, the slow transfer of oxygen across the placenta creates a relatively low level of oxygen in the fetal blood that actually stimulates growth. Premature delivery of the infant however, upsets this balance as a result of the supplemental oxygen given to such infants to sustain life. The adverse effects of elevated oxygen are especially severe on the retina, the light sensitive layer of the eye that is often less than 50% developed at the time of premature birth. Excessive oxygen in the vascular bed just beneath the retina diffuses into the undeveloped retina to retard its growth, reducing both neural and vascular development. As supplemental oxygen is eventually decreased, the reduction in oxygen supply combined with reduced blood flow and resurgence of retinal growth increases metabolic demand for more oxygen. The result is a condition called retinopathy of prematurity (ROP), characterized by the abnormal growth of retinal blood vessels that causes serious visual impairment or blindness. With 1:8 children born prematurely and a third of these affected by ROP, it has become the most common cause of childhood blindness in the United States. In children born before 27 weeks, three quarters are affected by ROP. Unfortunately, the retinal changes that occur in response to excessive oxygen are really only one sign of the adverse systemic health problems associated with organ system disabilities associated with premature birth, such as chronic asthma and the cerebral palsy. Today, strategies to cure ROP are aimed at blocking abnormal vessel growth after ischemia occurs. By contrast, Jonathan proposes to prevent ischemia before it induces proliferation of blood vessels. While restricting oxygen (hypoxic preconditioning) early in gestational age of premature infants reduces the risk of ROP and induces the normal development of the retina, Jonathan observed that protocol was accompanied by an increase infant death. His innovation is to “pharmacologically precondition” severely premature infants using a drug that induces the activity of an oxygen regulated transcription factor, hypoxia inducible factor (HIF), to control the development of blood vessels. He intends to do this by stabilizing HIF in order to recover its normal gene expression profile, which is altered by the effects of elevated oxygen; effectively “tricking” the premature retina into thinking it is exposed to its normal level of oxygen as a developing fetus. If Jonathan is successful, premature infants will retain the benefit of oxygen while avoiding ROP and the threat of lifelong blindness.