McCulley, David

The goal of Dr. McCulley's research program is to identify the genetic mechanisms that direct lung and pulmonary vascular development and physiological adaptation to birth. As a neonatologist he takes care of many infants who are born prematurely or who have anomalies that impair lung or pulmonary vascular development and function. Among the most challenging of these patients are infants born with congenital diaphragmatic hernia (CDH). CDH is one of the most common and most severe of all congenital malformations with a frequency of 1 in 3500 live births and a mortality rate of 20-50%. Babies with CDH have a hole in the diaphragm that allows the abdominal organs to herniate into the chest. Although surgical repair of the diaphragm can move the abdominal organs out of the thorax and provide room for the lungs to inflate, the lungs and pulmonary vasculature often do not develop or function normally. As a result many infants with CDH do not survive after birth due to lung hypoplasia and severe pulmonary hypertension. During his fellowship at the University of California, San Francisco he was mentored by Dr. Brian Black in the Cardiovascular Research Institute where he learned to use genetic tools to investigate cardiovascular development in mice. After moving to the University of Wisconsin-Madison, he was mentored by Dr. Xin Sun and applied the approaches he learned to study the developing lungs and pulmonary vasculature. Recently he has focused on identifying the genetic mechanisms responsible for lung and pulmonary vascular defects associated with CDH. Despite the frequency and severity of CDH, the genetic cause of the malformation and the mechanisms that lead to abnormal development and function of the lungs and pulmonary vasculature are poorly understood. In his recent work, he has used a combination of state-of-the-art genetic gain-of-function and loss-of-function experiments, in vivo physiology, and 2- and 3-dimensional histology to identify the genetic mechanisms responsible for abnormal lung and pulmonary vascular development associated with CDH. To conduct this research he collaborates with human geneticists who are conducting whole genome sequencing in patients with CDH. Using the results of these sequencing studies, he has generated new mouse models of CDH to identify the mechanisms of abnormal lung and pulmonary vascular development. He also collaborates with lung and pulmonary vascular physiologists to determine the functional consequences of the genetic mutations they have identified in human patients. His long-term goal is to continue investigating the basic mechanisms of lung and pulmonary vascular development related to CDH and preterm birth. By identifying the underlying mechanisms of abnormal development, he hopes to identify new therapeutic approaches that improve fetal and early postnatal lung development and function in pediatric patients. He plans to build a translational research program where their genetic mechanism studies will be used to devise novel and precise therapy for patients based on their individual genetic defect(s). He plans to carry out this work while serving as a mentor for both clinical and basic science research trainees who are pursuing careers in basic and translational biomedical research.