Sickle cell disease (SCD) and beta thalassemia affect over 180,000 Americans, and millions more worldwide. Both diseases can be ameliorated by increasing fetal hemoglobin (HbF) levels, but the only widely used HbF inducer, hydroxyurea, does not produce a clinical response in up to half of SCD patients, and is not effective in beta thalassemia. Our hypothesis, derived from unbiased analysis of whole exome sequencing data (WES) and robust functional studies in human erythroid precursor cells, is that metformin is an effective HbF inducing agent for individuals with hemoglobinopathies, either alone, or in combination with hydroxyurea in patients with SCD. The HbF inducing effect appears to be mediated through FOXO3, the gene identified as associated with HbF levels through rare variant analysis. We have designed a pilot study of metformin in patients with SCD on or off hydroxyurea, and in non-transfusion dependent beta thalassemia patients. This is an open label, single arm study. For patients with SCD, the primary endpoint will be increase in HbF. For beta thalassemia patients, the primary endpoint will be rise in total hemoglobin (Hb). Our trial has been approved by the Baylor College of Medicine Internal Review Board. We will also evaluate RNA expression changes in reticulocytes derived from patients before and on metformin, along with their genomic DNA, to better understand the mechanisms by which metformin achieves HbF induction, and leverage our existing whole exome sequencing data to investigate the pharmacogenomics of HbF response to metformin. We will assess patient blood for signs of rheological and vascular benefits of metformin, benefits observed in type II diabetics. Our work may lead to the first new oral HbF inducing agent in thirty years, and the first ever HbF inducing agent for beta thalassemia, revolutionizing the care of hemoglobinopathies worldwide.

Dr. Sheehan is an Assistant Professor of Pediatrics in the division of Pediatric Hematology/Oncology at Baylor College of Medicine. After completing a PhD in Biochemistry, Dr. Sheehan went on to medical school at Emory University School of Medicine; there, she decided to devote her career to sickle cell patient care and research. In order to care for people of all ages with sickle cell disease (SCD), Dr. Sheehan completed an Internal Medicine/Pediatrics residency program at the University of Cincinnati; she then completed a self-designed combined Internal Medicine Hematology-Pediatric Hematology/ Oncology fellowship. She is board certified in pediatric hematology/oncology and Internal Medicine Hematology. Dr. Sheehan's laboratory uses genomics to unravel the mechanisms of globin switching and the pharmacogenomics of hydroxyurea in SCD, in order to develop new fetal hemoglobin inducing agents. Her work has lead to a clinical trial of metformin as a fetal hemoglobin inducing agent in patients with hemoglobinopathies (FITMet: Fetal hemoglobin Induction with Metformin, NCT02981329). Dr. Sheehan also studies the effects of hydroxyurea and other sickle cell therapies on red cell density, deformability, migration through an artificial microvascular network and whole blood viscosity. Dr. Sheehan uses these four rheological tests to evaluate the effect of hydroxyurea on the blood of individuals with hemoglobin SC disease, as part of a phase II clinical trial (SC Youth Treatment Hydroxyurea Effects (SCYTHE), NCT02336373).