

ME Fabry, Bronx Comprehensive Sickle Cell Center: MRI and NIRS in SS Patients and Mice

The primary features of sickle cell disease are events resulting in low flow, poor perfusion, and blood and tissue hypoxia that are both pre-disposing to and the consequence of vaso-occlusion. We propose to test the limits of the hypothesis that the level of HbF, arginine in diet, and hydroxyurea all affect perfusion and blood oxygenation, albeit through different mechanisms. We will use a combination of Magnetic Resonance Imaging (MRI) and Near Infrared Spectroscopy (NIRS) to measure blood oxygenation, perfusion, and blood volume in human sickle cell patients and our new sickle transgenic mice that we have developed and characterized. At the onset of the grant period, our new Magnetic Resonance Research Center will have been in operation for more than 18 months with state-of-the-art 4 Tesla human and 9.4 Tesla animal systems. We have generated mice expressing exclusively human sickle hemoglobin with three levels of HbF using our previously described sickle constructs, mouse α - and β -globin-knockouts, and three different human γ -transgenes. We find that, progressive increase in HbF from <3% to 20% to 40% correlated with progressive increase in hematocrit (22% to 34% to 40%), a progressive decrease in reticulocyte count (from 60% to 30% to 13%), and an increase in lifespan (from 45 to 194 to 368 days). Using BOLD-MRI or blood level oxygenation dependent magnetic resonance imaging and T2 mapping, we have demonstrated that transgenic mice expressing high levels of human and β^S -globin have higher levels of deoxy Hb in brain, liver, and kidney, (areas showing pathology) compared to control mice. We also will measure a battery of other physiological properties including: reticulocytes, CBC, and red cell density, and, in the mice, rotorod performance (a measure of motor co-ordination and stamina) and urine concentrating ability. Finally, we propose that arginine may ameliorate the symptoms of sickle cell disease and will test this in humans and mice by measurement of flow and oxygenation as described in this Project and transport measurements described in the Arginine Supplementation in Sickle Cell Disease Project. Our long-range goal is to demonstrate that these technologies can be used for evaluation of pathology and prediction of risk in sickle cell disease patients.