Title: Strokes in children with sickle cell disease: Dynamic interplay between biomechanical and biochemical stimuli

Abstract: Arterial mechanics are associated with arterial damage, particularly due to remodeling of extracellular matrix, cellular composition, and vasoactivity. This has been examined in other cardiovascular diseases such as atherosclerosis, aging, and stroke. However, sickle cell disease-relevant literature on altered arterial mechanics and their causal link to extracellular matrix remodeling is sparse, particularly in light of the number of arterial complications due to sickle cell disease. Of children born with sickle cell disease, 11% will have a major stroke by age 16, and 30-35% will have a silent stroke impairing cognitive abilities. Later in life, risk for hemorrhagic stroke increases, suggesting an age-related component to arterial damage. Significantly higher velocities measured with transcranial Doppler in cerebral arteries implicates children at risk for strokes with disturbed cerebral hemodynamics. Cathepsins are a family of proteases containing the most potent human elastases and collagenases that we have shown to be upregulated by disturbed blood flow and by inflammatory stimuli, known to be elevated in sickle cell disease. It is unclear; however, how biomechanical and biochemical stimuli integrate to accelerate pathological remodeling of large arteries in these children. We will present our multiscale approach and results demonstrating these links between disturbed blood flow and chronic inflammation due to sickle cell disease, from the cellular level to transgenic animal models up through human computational fluid dynamics to identify new targets to prevent this accelerated artery damage affecting those born with this genetic disease and aging related implications.