

## Dipyridamole/Magnesium to Improve Sickle Cell Hydration

Karen Kalinyak, M.D. Principal Investigator  
Clinton H. Joiner, M.D., PhD Co-Investigator  
Robert D. Franco, PhD. Co-Investigator

Vaso-occlusive episodes are common among patients with sickle cell anemia (SCA), causing pain and chronic organ damage. SCA is characterized by the presence of dense, dehydrated sickle red blood cells (SS RBC), which rheologically abnormal and are selectively trapped during vaso-occlusion. Strategies to prevent cellular dehydration would offer important therapeutic options that might decrease vaso-occlusive episodes. SS RBC dehydration results from cation depletion mediated by two cation transport systems, a sickling-induced (SI) leak pathway and the KCl cotransporter (KCC). Previous work at this Center has shown that dipyridamole inhibits the SI fluxes of Na, K and Ca in vitro. Increasing cellular magnesium inhibits KCC activity and increases cellular hydration in animal models of SCA. A small clinical study in SCA patients demonstrated that Mg supplementation increase cellular Mg, reduced KCC activity and improved red cell hydration. This study will test the hypothesis that significant reduction in SS RBC dehydration will be seen in patients with SCA treated with either dipyridamole or magnesium. An additive, and possibly synergistic, effect on dense cell formation is hypothesized in patients treated simultaneously with both agents. A prospective, randomized, crossover, repeated measures design will be conducted among 48 patients with SCA, ages 12 years and older. Patients will be recruited from the Cincinnati Comprehensive Sickle Cell Center and the Sickle Cell Program at Wayne State University in Detroit. This design will allow for efficient comparison of the three treatment options; dipyridamole alone, magnesium alone or a combination of both. We anticipate that these therapies will be well tolerated by the patients. Primary outcome measures include the number of dense cells, assessed by automated cell counting and phthalate density gradients, cellular cation content, cell volume and hemoglobin concentrations. Using the biotin label technique pioneered in Cincinnati, measurements of red cell survival and rate of dense cell formation will be made in six patients in each treatment group, and will shed light on the mechanisms underlying SS RBC dehydration and is postulated inhibition by dipyridamole and Mg.