THE HARTWELL FOUNDATION

2020 Individual Biomedical Research Award

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Sickle Cell Disease Curative Therapy: Targeting Hemoglobin S Polymerization with Bifunctional Nongenomic Strands of RNA

Sickle-cell disease (SCD) is the most common genetically inherited blood disorder in the United States, with roughly 2,000 affected babies born each year. It is caused by a mutation in hemoglobin, the oxygen-carrying iron-containing protein within the red blood cell. The abnormal hemoglobin molecules in SCD (Hemoglobin S, HbS) combine to form a polymer in the red blood cell, which distorts the normal disk shape into a rigid crescent or *sickle* shape. This shape alteration prevents the cells from flowing smoothly through blood capillaries responsible for exchanging oxygen in tissues, causing significant pain, depriving the lungs, kidneys, spleen, and brain of oxygen rich blood, and may cause irreversible organ failure. In addition, the sickle shaped red blood cells are not flexible and break down more easily, which contributes to anemia, fatigue and delayed growth and development in children. Children with SCD face long-term chronic and debilitating symptoms of pulmonary hypertension, ulcers, stroke, vision loss, a lower quality of life and a shortened lifespan. Children affected by SCD miss more school than their healthy peers due to pain crises, hospitalizations, and other complications, further disadvantaging them in their life trajectory. The incidence of sickle cell trait varies greatly among different races and ethnicities but is highest among African Americans and Hispanic Americans. The most common intervention for SCD is an oral generic drug called hydroxyurea, a therapy that helps the body keep producing another form of hemoglobin (called fetal hemoglobin), which isn't affected by sickle cell disease. However, a host of adverse off-target side effects often limits the effectiveness of the drug in many patients. The only cure for SCD is a bone marrow transplant, but less than 18 percent of children qualify for this procedure due to the lack of a compatible donor match, which means that most pediatric patients are treated only for the complications of SCD. To address this dire need for a specific and effective therapeutic option, Yolanda recently identified novel molecules based on nongenomic strands of RNA (aptamers) that inhibit the polymerization of Hemoglobin S, in vitro. On this basis, I propose to develop a curative therapy for SCD using aptamers that will effectively block the polymerization and prevent the formation of sickled red blood cells, in vivo. Her strategy focuses on development of an aptamer delivery system based on an artificial bivalent molecule with two functional activities: an intracellular aptamer that when favorably internalized will release an inhibitory aptamer that will impede hemoglobin polymerization and block cell sickling. To minimize off target effects, she will optimize aptamer selectivity for red blood cells and the effectiveness of the aptamer internalization process, by varying aptamer size, affinity, and specificity. If successful, the curative potential of RNA aptamers in SCD will provide a direct therapeutic benefit for affected children, which will improve and extend the quality of their lives.