AREA OF FOCUS #4

Sickle Cell Disease

Sickle cell disease is a generic term for a group of genetic disorders characterized by the predominance of hemoglobin S (Hb S). In the United States, these disorders are most commonly observed in African Americans and Hispanic Americans from the Caribbean, Central America, and parts of South America. It affects nearly one of every 600 African Americans.

Tissue injury is usually produced by hypoxia secondary to the obstruction of blood vessels by an accumulation of sickled erythrocytes. Symptoms of the hypoxic injury may be either acute (e.g., painful events, acute chest syndrome) or insidious in onset (e.g., aseptic necrosis of the hips, sickle cell retinopathy). The effects of acute and chronic tissue injury may ultimately result in failure of organs like the kidney, particularly as the patient ages.

Sickle cell anemia and its complications (e.g., painful hemolytic anemia crises; strokes; lung, heart, and kidney diseases) are a major cause of morbidity and premature mortality in African Americans.

While the molecular basis of sickle cell disorders has been well characterized, cure of this disease has not been realized to date.

Drugs that increase production of red blood cells and normal hemoglobin have decreased the morbidity of sickle cell disease. Recent research suggests that drugs such as nitric oxide that increase oxygenation and blood flow through critical organs may decrease the complications of sickle cell disease.

Preliminary studies indicate that stem cell transplantation (and possibly gene therapy) offers potential cures for sickle cell anemia.

Research Goal

To improve understanding of sickle cell disease, its treatment, and prevention of its complications

Current Activities

There is a portfolio of current investigations aimed at the regulation of fetal globin gene transcription in a stage-specific manner and the identification of molecules that may be used as drugs to enhance the levels of fetal hemoglobin in the circulating red blood cells of children and adults with hemoglobin disorders.

Studies in NIDDK's intramural research program have shown that drugs that increase production of red blood cells and normal hemoglobin have improved the well-being of patients and decreased the morbidity of sickle cell disease. Other recent research findings indicate that drugs, such as nitric oxide, that increase oxygenation and blood flow through critical organs may decrease the complications of sickle cell disease. Preliminary studies have begun to examine whether stem cell transplantation (and possibly gene therapy) offers potential cures for sickle cell anemia.

Potential New Initiatives

1. **Study drugs that modulate production of normal adult hemoglobin, characterize the physiologic effects and clinical benefits of nitric oxide, and explore the use of allogeneic stem cell transplantation for correction of sickle cell anemia.**

Action Plan
Investigations will be carried out in the intramural program.

2. **Control fetal globin gene expression and develop approaches for therapeutic induction of fetal globin genes.**

The purpose of this initiative is to stimulate new avenues of research into the developmental processes involved in the differential expression of globin genes. The emphasis is on understanding the mechanisms of regulation of fetal hemoglobin synthesis and the development of new approaches of stimulation of fetal hemoglobin in patients with sickle cell anemia and other beta chain hemoglobinopathies by the following:

- Identification and characterization of genetic, molecular, and cellular factors involved in the developmental regulation of the fetal and embryonic globin genes.
- Investigation of the mechanisms involved in the activation and silencing of the fetal globin genes.
- Studies of the linkage between erythroid cell differentiation and the developmental control of the globin genes.
- Examination of the relationship between globin gene expression and the signal transduction mechanisms that are involved in erythroid cell maturation.
- Determination of the mechanism of action of drugs, such as hydroxyurea and butyrate, that affect fetal hemoglobin (HbF) levels.
- Discovery of new classes of compounds that can induce fetal hemoglobin in cultures of primary erythroid cells and in animal models.
- Development of new model systems to study the regulation of fetal globin genes.

Expected Outcome

This initiative, if successful, will improve treatment of African Americans with sickle cell disease, reducing morbidity and mortality by increasing the amount of functional hemoglobin in circulation.

Action Plan

Solicitation will include requests for R01 grant applications (RFAs).

Public Information and Outreach Goal

To increase awareness about treatment of sickle cell disease in African Americans

Current Activities

The National Heart, Lung and Blood Institute (NHLBI) disseminates information about sickle cell disease. Existing publications include *Facts About Sickle Cell Anemia*, also translated into Spanish, and the fact sheets *Hydroxyurea in Pediatric Patients with Sickle Cell Disease* and *The Multicenter Study of Hydroxyurea in Sickle Cell Anemia*.

Potential New Initiative

None.

Action Plan

Work with NHLBI and public and private partners representing African Americans to identify additional information needs of patients, families, and physicians and distribute the available information to the communities.