GDF15, a Marker and Cause of Morbidity in Thalassemia

Description of Technology:

The invention relates to methods to measure the Growth Differentiation Factor 15 (GDF15, also known as MIC-1 or NAG-1) levels in order to diagnose or predict disease severity in patients with thalassemia and with related complications to, treat thalassemia by administration of a GDF15 antagonist, and to reduce hepcidin levels by administration of GDF15, a GDF15 substitute, or GDF15 agonist.

Thalassemia consists of a group of inherited diseases of the red blood cells, arising from deficient or absent production of globin chains. In beta-thalassemia, also known as Cooley's anemia or Mediterranean anemia, defective globin production reduces the number and viability of red blood cells, causing anemia and subsequent expansion of bone marrow. As a result of marrow expansion, distorted bone formation ensues. Beta thalassemia, the most severe form of thalassemia, also results in iron overload, which is the major cause of beta-thalassemia mortality worldwide. As a result of iron overload, the patient may develop hypopituitarism, hypothyroidism, hypoparathyrodism, diabetes, arthropathy, cirrhosis and cardiopulmonary disease. Treatment of beta-thalassemia involves frequent blood transfusions and chelation therapy to remove excess iron from the blood.

In thalassemia, the patient's hepcidin expression is pathologically suppressed. Hepcidin is a protein, synthesized in the liver, that reduces iron absorption in the body. The inventors have identified GDF15 as a hepcidin suppressing cytokine that is overexpressed in thalassemia. GDF15 is a member of the TGF-Beta superfamily of proteins, which are known to control cell proliferation, differentiation, and apoptosis in numerous cell types. GDF15 levels in blood plasma have been found to be dramatically elevated in beta-thalassemia patients compared to healthy donors and patients with hereditary hemochromatosis, another form of iron overload disease. In addition, the role of GDF15 in other disorders characterized by ineffective erythropoiesis, as well as the role of GDF15 in the regulation of iron metabolism is under investigation.

Applications:

- Diagnostic test to detect increased risk for thalassemia-related complications
- Treatment of thalassemia by administration of a GDF15 antagonist
- Treatment of iron-dysregulated diseases
- Treatment of ineffective erythropoiesis
- Treatment of anemia of chronic disease

Market:

Thalassemia is a growing global public health problem. It is estimated that seven percent of the world's population are carriers with about 400,000 affected babies born each year. Approximately 1,000 people in the United States currently have beta-thalassemia, however the number of affected individuals is expected to grow. Prevalence of the disease is higher in those of Mediterranean descent and those from China, India and other Asian countries. The U.S. F.D.A classifies thalassemia as a rare or orphan disease.

Companies interested in the development of diagnostics for the detection of thalassemia-related complications, as well as the development of alternative therapeutics directed toward the treatment of anemias including thalassemia or other diseases involving bone and iron dysregulation, may be interested in this technology.

Development Status:

Early stage

Inventors:

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Publications: *In Review*

Patent Status:

DHHS Reference No. E-022-2007, a provisional application has been filed.

Licensing Status:

Available for exclusive or nonexclusive licensing

Licensing Contact:

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Collaborative Research Opportunity:

The NIDDK's Molecular Medicine Branch is seeking parties interested in collaborative research to further develop, evaluate, or commercialize the role of GDF15 in chronic anemias characterized by ineffective erythropoiesis, as well as the role of GDF15 in the regulation of bone and iron metabolism. Please contact Dr. Jeffery L. Miller at Jeff.Miller1@nih.hhs.gov or Rochelle S. Blaustein at Rochelle.Blaustein@nih.gov for more information.

Research Focus and Selected Publications for Principal Investigator

Jeffrey Lynn Miller, M.D., Molecular Biology and Genetics Section

The laboratory is focused upon the determination of molecular mechanisms responsible for diseases involving erythroid cells. A variety of laboratory and bioinformatic approaches are applied directly to the study of human blood stem and progenitor cells. Molecular and genomic studies from the laboratory are then correlated with clinical data for disease prevention or the development of genetic and pharmaceutical therapies.

1. Goh SH, Lee YT, Bhanu NV, Cam MC, Desper R, Martin BM, Moharram R, Gherman RB, Miller JL A newly discovered human alpha globin gene. *Blood*, 2005. [Full Text/Abstract]

2. Bhanu NV, Trice TA, Lee YT, Gantt NM, Oneal P, Schwartz JD, Noel P, Miller JL A sustained and pancellular reversal of gamma-globin gene silencing in adult human erythroid precursor cells. *Blood*(105): 387-93, 2005. [Full Text/Abstract]

3. Miller JL Signaled expression of fetal hemoglobin during development. *Transfusion*(45): 1229-32, 2005. [Full Text/Abstract]

4. Miller JL A genome-based approach for the study of erythroid biology and disease. *Blood Cells Mol Dis*(32): 341-3, 2004. [Full Text/Abstract]

5. Bhanu NV Trice TA Lee YT Miller JL A signaling mechanism for growth-related expression of fetal hemoglobin. *Blood*(103): 1929-33, 2004. [Full Text/Abstract]