Novel Therapeutics for Treatment of Acute Chest Syndrome

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Technology description

Market Summary

Sickle cell anemia affects around 72,000 persons in the U.S. Acute chest syndrome is an acute pulmonary illness that is a complication of sickle cell anemia. It is a common cause of hospitalization and death for sickle cell patients. There are 12.8 ACS episode/100 patient years in the United States in patients with homozygous disease with children age 2-4 having the highest incidence. Current treatment includes supportive care, antibiotics, bronchodilators, incentive spirometry, and transfusion. None are curative so there is a need for novel therapies. Novel therapies will most likely qualify for orphan drug status and orphan drug molecules for rare diseases had sales between $400-$800M in 2009.

Technical Summary

At the time of diagnosis of ACS, nearly all patients experience a decrease in hemoglobin concentration. This drop in hemoglobin levels acutely elevates the circulating pool of cell-free hemoglobin and heme, the iron containing component of hemoglobin, and results in oxidative damage that leads to the clinical symptoms of ACS. A protective mechanism exists in the body through a protein known as hemopexin, which binds heme with the highest affinity of any known protein, scavenges free heme and prevents oxidative damage. Â Emory researchers have developed a mouse model of ACS where an intravenous injection of free heme will acutely elevate plasma concentration of cell free hemoglobin and heme and trigger ACS and eventually death if left untreated. These researchers have also found that administration of recombinant hemopexin can prevent ACS related death in this mouse model. Experimental findings also suggest that in this mouse model, hemin (ferric heme) binds to TLR4 on pulmonary epithelial cells and activates NF-kappa B which triggers acute inflammation and hypoxia that leads to ACS. Therefore, TLR4 may also be a good drug target or ACS. Heme-induced death has been shown to be dependent on expression of TLR4 through experiments in mice that lack TLR4 activity due to a deletion or mutation of the gene. Further experiments show that administration of a TLR4 inhibitor like TAK-242 reduces mortality by almost 50% in this mouse model of ACS.

Application area

Potential therapeutic for the treatment of acute chest syndrome (ACS), an acute respiratory distress complication of sickle cell anemia.

Advantages

Current therapies for acute chest syndrome are supportive only so there is a need for novel therapies. Toll-like receptor 4 (TLR4) inhibitors and hemopexin, a naturally-occurring recombinant protein, have been found to reduce mortality in a mouse model of ACS and may offer a curative option for this syndrome.

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