Treatment and Prevention of White Matter Injury with Diazoxide and KATP Channel Activators

**OCR Number:** OCR 5116

**Description:**
One of the commonest forms of brain injury in newborn infants is Periventricular White Matter Injury (PVMI) which is associated with preterm delivery and low birth weight. In the United States approximately 100,000 infants are born each year with risk of developing PWMI, of which about 25% will develop the disorder. PWMI is associated with significant morbidity with affected individuals prone to intellectual impairment and cerebral palsy. Oligodendrocytes are the myelinating cells of the Central nervous System (CNS) and are particularly vulnerable to hypoxia at this developmental stage which can lead to reduced numbers of oligodendrocytes and thereby hypomyelination of nerve fibres in the developing brain. Researchers at Yale University have identified a pharmacological mechanism whereby proliferation of oligodendrocytes can be stimulated by activation of ATP-dependent potassium channels (KATP channel) in the plasma membranes of oligodendrocytes. Small molecular weight candidate therapeutic compounds (e.g., Diazoxide) have been identified which activate the KATP channel and which have been shown not only to promote proliferation of oligodendrocyte precursor cells in culture but also to increase myelination in rat brain slices in vitro and to prevent hypomyelination and ventriculomegaly in vivo in newborn mice subjected to chronic sub-lethal hypoxia. One of the KATP channel activators shown to mediate the effect on myelination has also been used therapeutically in infants to treat hyperinsulinemic hypoglycemia.

**Value Proposition:** In the United States alone approximately 400,000 infants are born prematurely each year. Of these about 100,000 are at risk of PWMI and about 25,000 will develop significant morbidities associated with this pathology. Currently there is no established treatment for PWMI so any novel approach would fill a considerable unmet medical need, and would have a major health economic impact since affected individuals require medical and social support throughout their lives.

**Field of Application:** Clinical development of small molecular weight therapeutics for the treatment and/or prevention of PWMI.

**Advantages:** Currently there is no established treatment for PWMI so a clear unmet medical need exists. Since one of the compounds identified is already established for the treatment of hyperinsulinemic hypoglycemia in infants, the development in the PWMI indication may be facilitated by virtue of the existing clinical experience. Furthermore, any risk associated with the clinical development of this compound class in newborns is hedged to some degree as the compound has a history of effective and safe treatment in infants.

**Stage of Development:** Research stage with proof of concept achieved in animal models.


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