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OP-101: A novel therapy for treatment of childhood cerebral adrenoleukodystrophy

X-linked adrenoleukodystrophy (ALD) is an ultra-rare disorder (incidence of 1:17,000 males) caused by mutation of the ABCD1 gene, resulting in high levels of circulating very long chain fatty acids (VLCFA). The childhood cerebral form (ccALD) occurs in ~35% of X-ALD boys between the ages of 2-10 years, and is characterized by oxidative stress, neuroinflammation and microglial activation leading to a rapidly progressive cerebral demyelination fatal within 2-3 years. Hematopoietic stem cell transplant (HSCT), the only currently approved therapy, is effective in arresting neuroinflammation and demyelination only if provided early. There is a crucial need for therapies for patients who are diagnosed late or are not eligible for HSCT (~50% patients), and for arresting disease progression during HSCT. Rapid progression of neuroinflammation as characterized by MRI imaging correlates with loss of neurological function. Gadolinium enhancement on MRI indicating an impairment of the blood brain barrier (BBB) is a characteristic feature in rapidly progressing ccALD. Therefore, reducing or inhibiting neuroinflammation caused by activated microglia can lead to disease stabilization in ccALD patients not eligible for HSCT. OP-101 is a new chemical entity consisting of N-acetyl cysteine (NAC) covalently coupled to a metabolically- stable inactive dendrimer. Studies in several small and large pre-clinical models have demonstrated the selective endocytosis uptake of OP-101 by activated microglia/ and astrocytes upon intravenous administration, localizing only in brain regions where there is with neuroinflammation-induced BBB impairment of the blood brain barrier. OP-101 releases NAC intracellularly in activated microglia and astrocytes, which then acts to reduce the attenuating oxidative stress and inflammation, in these cells and leads producing to significant improvements in neurobehavioral outcomes in the preclinical models, unlike the free drug. Macrophages isolated from ccALD patients and stimulated with VLCFA have significantly reduced cytokine expression and glutamate secretion with increased glutathione levels, when treated ex vivo with OP-101. Pilot toxicity studies in juvenile rats show that no toxicity of OP-101 is safe at doses as high as even at 1000 mg/kg IV QOD. A phase 1/2/3 placebo controlled trial for patients with ccALD who are not eligible for HSCT is planned to start in 2018.

Biography

Sujatha Kannan MD is an Associate Professor in Anesthesiology and Critical Care Medicine and Co-Director of the Pediatric Neurocritical Care Program at the Charlotte Bloomberg Children's Center at Johns Hopkins University, Baltimore, MD. She is also the CMO of Orpheris Inc. Orpheris is focused on the treatment of neuroinflammatory orphan diseases that result in death or severe disabilities, ccALD, neonatal brain injury, Huntington's disease, Rett syndrome and autism spectrum disorders. Orpheris' patented hydroxyl dendrimer technology selectively targets inflammation in injured glial cells implicated in a number of brain diseases. Controlling inflammation through targeting injured glia with OP-101 is a potent weapon against CNS disorders. OP-101 is the company's first potential drug candidate utilizing hydroxyl dendrimer technology to deliver therapeutic doses of an anti-inflammatory drug across the blood brain barrier to reduce inflammation in glial cells.

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