Synopsis of GCSF gene therapy for stroke and Alzheimer's disease

Granulocyte colony-stimulating factor (GCSF) is an FDA-approved drug for enhancing blood cell formation. We as well as others have shown that GCSF has neuroprotective properties in animal models of stroke, Parkinson diseases (PD), Alzheimer's disease (AD) and other neurodegenerative diseases. Protein therapy using GCSF is attractive because GCSF is well tolerated after systemic delivery. However, its plasma half - life is about 4 hours; moreover, there is potential for chronically elevating white blood cells during repeated delivery. To circumvent the limitation associated with protein therapy, we have developed a GCSF gene therapy for stroke and AD using adenovirus vectors, (AAV-GCSF), that would provide a sustainable level of GCSF over a long period of time under regulated condition such as in a specified cells or under a specified physiological condition such as hypoxic condition. We have demonstrated the efficacy of AAV-GCSF gene therapy for stroke and AD in animal models as indicated in marked improvement in brain functions at molecular/cellular and behavioral levels as detailed in our recent International Patent Application entitled " Granulocyte colony-stimulating factor (G-CSF) gene therapy for treating neurological diseases " (EFSID: 36063150; International Application Number: PCT/US19/33124 ; Filed: May 20, 2019;Inventor: Jang-Yen Wu).

Innovation:

One of the innovations of AAV-GCSF gene therapy for stroke and AD is that we have developed a new and innovative two-pronged approach to preserve and/or restore the function of the brain by first protecting the brain against stroke- or AD-induced injury and secondly, by stimulating neurogenesis to replenish new brain cells using a well-regulated GCSF gene therapy. The innovation of the AAV-GCSF gene therapy is four-fold. Firstly, the delivery method of AAV-GCSF gene vector by eye drop is simple and effective as validated by the verification of human GCSF (hGCSF) mRNA and hGCSF protein in the brain of both stroke and AD animal model. Secondly, the level of GCSF expression in stroke or AD is well regulated since the vector to be used includes a hypoxia response element, HRE, as the promoter domain which is regulated by the stroke-related hypoxic condition. The use of the HRE promoter containing vector will ensure that expression does not occur in cells that are normal, and that expression is localized to the hypoxic regions. Thirdly, unlike the exogenously administered GCSF protein which has a short half-life of only 4 hours, the expression of GCSF from the delivered GCSF gene could last months or even years providing the patients with sustainable supply of GCSF during the recovery process. Fourthly, adenovirus vectors have been widely used for gene therapy and vaccination. Many clinical trials indicate that replication-defective and replication-competent adenovirus vectors are safe and have therapeutic activity. In fact, the U.S. Food and Drug Administration approved Luxturna (voretigene neparvovec-rzyl) on December 18, 2017, a new gene therapy using AAV 2 adenovirus as vector, the same as used in our AAV-GCSF vector, to treat children and adult patients with an inherited form of vision loss that may result in blindness.

Impact:

This AAV-GCSF gene therapy that we developed will have the potential to bring us closer to developing an optimal intervention for the treatment for stroke and Alzheimer disease AD. Once the stroke and AD treatment is shown to be effective, we should then be in a better position to offer gene therapy to other diseases in the future. Hence the impact could be quite broad and significant in disease treatment and assessment of the outcome of the treatment.