TREM2MICROENGINES - TREM2 MICROglia ENGENEering for treating dementiaS

The project TREM2MICROENGINES aims to demonstrate that raising and restoring TREM2 expression in the brain of Alzheimer's disease (AD) and Nasu–Hakola disease (NHD) patients, and in particular in their microglia, would result in therapeutic benefit. AD is a severe neurodegenerative disorder that represents the most frequent form of dementia among the elderly which affects approximately 5.1 million Americans and this number is supposedly tripled by 2050. AD is believed to result from the deposition of extracellular amyloid-β (Aβ)-containing plaques. TREM2-Triggering receptor expressed on myeloid cells 2 is a microglia cell-surface receptor whose deficiency or haplo-insufficiency augments Aβ accumulation due to a dysfunctional response of cells, which become apoptotic. Homozygous, loss-of-function mutations in TREM2 also cause the autosomal recessive disorder NHD, a ultra-rare inherited disease of the white matter (WM) with typical onset in the adult age, and pathophysiologically characterized by microglial dysfunction (microgliopathy). The key clinical feature of NHD is progressive presenile dementia usually leading to death in the fifth decade of life NHD patients also lack curative treatments. A relevant proportion of AD cases and all forms of NHD are caused by pathogenic mutations in the Trem2 gene which lead to microglia dysfunction contributing to and/or causing the onset and manifestations of AD and NHD. Based on this provision, our working hypothesis is that transplantation of HSCs engineered by LVs to express robust TREM2 levels in response to tissue damage in CNS-engrafted myeloid/microglia cells would modulate neuroinflammation, restore physiological microglia functions and contribute preventing and reducing Aβ accumulation in the CNS of AD and NHD patients. No existing approaches currently allow targeting microglia dysfunction in AD or in NHD, nor at enhancing microglia specific function through a microglia-targeted TREM2 delivery/engineering.

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