Credit: Stocktrek Images, Inc./Alamy Stock Photo

“levels of DNTs were elevated in the blood of patients following ischaemic stroke”

By blocking the FasL–PTPN2–TNF signalling pathway in mice, the team was able to ameliorate ischaemic brain injury, and they propose that this pathway could be targeted pharmacologically to improve outcomes after ischaemic stroke.

Heather Wood

ORIGINAL ARTICLE Meng, H. et al. Double-negative T cells remarkably promote neuroinflammation after ischemic stroke. *Proc. Natl Acad. Sci. USA* <https://doi.org/10.1073/pnas.1814394116> (2019)

injury, or whether they individually contributed to cognition, suggesting a unique pathway of injury,” explains Jefferson.

By examining the imaging markers in combination, the researchers found that WMH, PVS and CMBs were all independently associated with information processing and executive function. However, PVS showed associations with executive function and information processing speed performances beyond the other markers, suggesting that they might contribute to adverse cognitive health through a unique pathway.

“The findings need to be replicated in a different cohort of ageing participants to confirm the results,” says Jefferson. “We need to refine our measurement of enlarged PVS and other markers of small vessel disease and better understand the aetiologies of these markers.”

Rebecca Kelsey

ORIGINAL ARTICLE Passiak, B. S. et al. Perivascular spaces contribute to cognition beyond other small vessel disease markers. *Neurology* <https://doi.org/10.1212/WNL.00000000000007124> (2019)

“PVS ... might contribute to adverse cognitive health through a unique pathway”

ALZHEIMER DISEASE

Alzheimer disease mice improve with CRISPR–Cas9 gene editing

CRISPR–Cas9 gene editing has successfully been used to reduce pathology and behavioural impairments in mouse models of Alzheimer disease (AD) in a new study published in *Nature Neuroscience*. The work could pave the way to gene-editing approaches to treatment of the disease.

In vivo gene editing in post-mitotic cells, such as neurons, with the CRISPR–Cas9 system has not been perfected, and virus-mediated CRISPR–Cas9 gene editing is associated with problems owing to integration of vectors into the host genome. In work to develop treatments for neurodegenerative disease, Jongpil Kim and colleagues have made progress towards addressing both problems through the use of nanotechnology.

“Previously, we developed novel CRISPR–Cas9 nanocomplexes that can lead to efficient gene targeting in post-mitotic neurons of the adult mouse brain without genomic integration and with very low cytotoxicity,” Kim explains.

The nanocomplexes consisted of the Cas9 protein, single-guide RNA (sgRNA) that targets Cas9 to the intended gene, and R7L10 micelles. These micelles can mediate delivery of the complexes into cells, thereby avoiding the need for virus-mediated delivery.

After confirming that the nanocomplexes caused minimal toxicity in mouse fibroblasts, Kim and colleagues used sgRNAs to successfully target nanocomplexes to specific genes in mouse primary neurons. The targeted genes included *Bace1*, which encodes β -secretase 1. This enzyme is required for the production of amyloid- β (A β) peptides and, therefore, has a central role in the accumulation of A β that occurs in AD.

The researchers then tested their approach in live mice and showed that injection of targeted nanocomplexes into the brains of wild-type animals reduced expression of the targeted proteins without causing inflammatory responses, toxicity or apoptosis. On this basis, they finally tested *Bace1*-targeted nanocomplexes as an approach to AD therapy in mouse models of the disease.

In the five familial AD (5xFAD) model, treatment with the Cas9 nanocomplexes reduced production of A β and improved performance in cognitive tests compared with non-treated mice. The improvements were maintained at 12 weeks after treatment. Similar pathological and cognitive benefits were seen with nanocomplex treatment in the amyloid precursor protein knock-in mouse model of AD.

Genome sequencing showed that off-target effects of the Cas9 nanocomplexes were minimal. Mutation rates did not differ between treated and non-treated animals, suggesting that the therapeutic approach is safe. However, clinical translation of the approach requires considerable work.

“We need to develop more cell-type-specific delivery systems for Cas9 nanocomplexes that enable intravenous delivery to the appropriate brain region,” says Kim. “Moreover, gene editing is irreversible and, thus, caution must be exercised to ensure no detrimental effects. We now plan to test our strategy in larger animal models for long-term safety studies.”

Ian Fyfe

ORIGINAL ARTICLE Park, H. et al. In vivo neuronal gene editing via CRISPR–Cas9 amphiphilic nanocomplexes alleviates deficits in mouse models of Alzheimer’s disease. *Nat. Neurosci.* <https://doi.org/10.1038/s41593-019-0352-0> (2019)