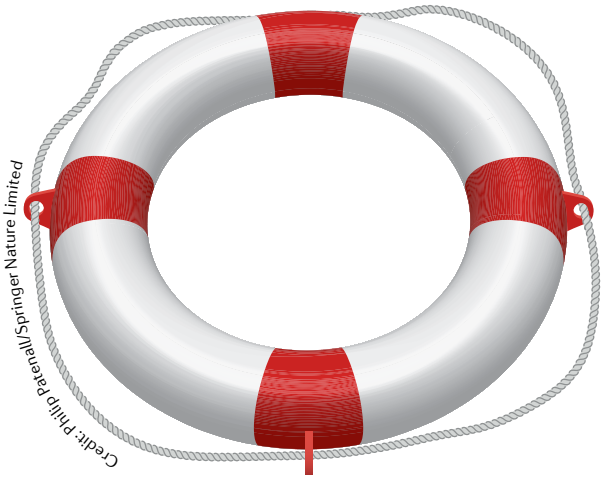

multiple sclerosis, and the findings of Barak et al. suggest that this drug could be repurposed for Williams syndrome.

"Our findings shed new light on the role of *Gtf2i* in regulating neuron–oligodendrocyte interactions and myelination," concludes Barak. "We now plan to further explore the molecular and transcriptomic alterations in different cell types in the mouse brain as a result of *Gtf2i* deletion in neurons."

Heather Wood

> clemastine … rescued both the myelination defect and the behavioural phenotype

ORIGINAL ARTICLE Barak, B. et al. Neuronal deletion of *Gtf2i*, associated with Williams syndrome, causes behavioural and myelin alterations rescuable by a remyelinating drug. *Nat. Neurosci.* **22**, 700–708 (2019)

action potential (CMAP) and quantitative multipoint incremental motor unit number estimation.

Over the 3 years, mean scores in the motor function measures improved, and CMAP amplitude and area remained generally stable. "The results confirm prior findings but also provide evidence for longer-term efficacy and safety in an extended age range of patients," says Darras.

Furthermore, average motor function continued to improve throughout the 3 years of follow-up. "These results provide evidence for continued improvements over time, which is a novel finding," states Darras. The researchers now intend to continue monitoring patients who are participating in a long-term safety study.

Ian Fyfe

> These results provide evidence for continued improvements over time, which is a novel finding

ORIGINAL ARTICLE Darras, B. T. et al. Nusinersin in later-onset spinal muscular atrophy. *Long-term results from the phase ½ studies. Neurology* https://doi.org/10.1212/WNL.0000000000007527 (2019)
FURTHER READING Groen, E. J. et al. Advances in therapy for spinal muscular atrophy: promises and challenges. *Nat. Rev. Neurol.* **14**, 214–224 (2018)

ALZHEIMER DISEASE

Age-related microglial activation accelerated in AD

Amyloid-β (Aβ) pathology accelerates age-related expansion of activated microglial populations, according to a new study published in *Cell Reports*. The effect was influenced by sex and genetic risk factors for Alzheimer disease (AD) and could provide novel therapeutic targets.

The pathological hallmarks of AD — amyloid-β plaques and tau tangles — are accompanied by extensive cellular changes, including the development of so-called disease-associated microglial phenotypes. Microglia also express many of the known AD risk genes, indicating that they have a central role in the pathogenesis of the disease. The new study, led by Carlo Sala Frigerio and Bart De Strooper, investigated how ageing and progressive Aβ accumulation influence the gene expression profiles of individual microglial cells.

"We believe that to successfully identify a therapy for AD, we need to identify how the numerous different brain cell types react to formation of Aβ plaques and neurofibrillary tangles," explains Sala Frigerio. "Extensive data from genetic association studies have indicated a preponderant role of microglia in the risk of developing AD, therefore we focused our attention on this cell type."

The team used single-cell RNA sequencing to analyse the gene expression profiles of microglia from *App* knock-in mice, which display progressive deposition of Aβ, and from wild-type controls. Individual microglia were isolated from the hippocampus and cortex of mice at four different ages. The team then performed a clustering analysis to identify subpopulations of microglia with similar gene expression profiles.

> the age-related increase in these activated microglia — particularly ARMs — was greatly accelerated by Aβ accumulation

The analysis identified that transcriptomic changes occur with normal ageing and lead to two main activated microglial states — activated response microglia (ARMs) and interferon response microglia (IRMs). However, the age-related increase in these activated microglia — particularly ARMs — was greatly accelerated by Aβ accumulation in the *App* knock-in mice. "ARMs thus constitute a canonical response to age-dependent brain tissue alteration, and their development is enhanced by Aβ deposition," explains Sala Frigerio.

The researchers also looked at differences between male and female mice, and found that conversion of homeostatic microglia to the IRM or ARM reactive states progressed faster in females than in males. "This finding is of relevance for AD, since clinical studies point to a higher susceptibility for AD in women," says Sala Frigerio.

In the ARMs cluster, genes associated with AD were strongly enriched, including upregulation of *Apoe*. Analysis of microglia isolated from a different mouse model of AD showed that *Apoe* deletion impaired the increase in ARMs in response to Aβ accumulation that was seen in *App* knock-in mice. Finally, analysis of bulk tissue from human brains showed that the genes upregulated in the ARMs cluster in mice were also upregulated in individuals with a high Aβ plaque burden.

The new insights into the connection between specific microglial subsets and AD pathology could inform the search for therapeutic targets. "Now we need to understand how human microglia behave during AD pathology, and to what extent mouse microglia effectively model human microglia," notes Sala Frigerio. "This is of paramount interest in the quest for developing an efficient drug for AD."

Sarah Lemprière

ORIGINAL ARTICLE Sala Frigerio, C. et al. The major risk factors for Alzheimer's disease: age, sex and genes modulate the microglia response to Aβ plaques. *Cell Rep.* **27**, 1293–1306 (2019)