IN BRIEF

PERIPHERAL NEUROPATHIES

FDA approves patisiran to treat hereditary transthyretin amyloidosis

As recently reported in *Nature*, the RNA interference (RNAi) drug patisiran has been approved by the FDA for the treatment of hereditary transthyretin amyloidosis (hATTR). hATTR is a genetic condition that is characterized by accumulation of misfolded transthyretin (TTR) protein in multiple organs and systems, including the nervous system. Patisiran works by targeting *TTR* mRNA to inhibit the production of mutant TTR, and is the first RNAi therapy to be approved by the FDA. The approval of patisiran represents the culmination of two decades of RNAi research, and is an important milestone not only for the treatment of rare disorders such as hATTR but also for RNAi therapy in general.

ORIGINAL ARTICLE Ledford, H. Gene-silencing technology gets first drug approval after 20-year wait. *Nature* **560**, 291–292 (2018)
FURTHER READING Fyfe, I. Treatment success in hereditary transthyretin amyloidosis. *Nat. Rev. Neurol.* https://doi.org/10.1038/s41582-018-0048-1 (2018)

NEURO-ONCOLOGY

Addition of bevacizumab fails to improve on temozolomide alone for glioma therapy

In patients with grade II or grade III glioma, bevacizumab administered in combination with temozolomide confers no additional survival advantage over temozolomide alone, according to a phase II trial published in *The Lancet Oncology*. The open-label TAVAREC trial enrolled 155 patients who had recurrent grade II or grade III glioma without chromosome 1p and 19q co-deletion — a tumour subclass that often responds poorly to chemotherapy. The participants were randomly assigned to receive temozolomide plus bevacizumab or temozolomide alone. The addition of bevacizumab to temozolomide chemotherapy did not significantly improve overall survival or progression-free survival at 12 months, and the researchers concluded that bevacizumab does not warrant further exploration as a treatment for this glioma subclass.

ORIGINAL ARTICLE van den Bent, M. J. et al. Bevacizumab and temozolomide in patients with first recurrence of WHO grade II and III glioma, without 1p/19q co-deletion (TAVAREC): a randomised controlled phase 2 EORTC trial. *Lancet Oncol.* https://doi.org/10.1016/S1470-2045(18)30362-0 (2018)

MOTOR NEURON DISEASE

A potential biomarker strategy to monitor treatment response in spinal muscular atrophy

With the emergence of new therapies for spinal muscular atrophy (SMA) — most notably, the antisense oligonucleotide nusinersen — objective longitudinal measures of treatment response are becoming increasingly important. SMA is caused by mutations in the survival motor neuron 1 (*SMN1*) gene, which result in a lack of functional SMN protein. A team from Japan has now developed a blood test that can differentiate between patients with SMA and healthy control individuals on the basis of SMN expression levels. Using imaging flow cytometry combined with more detailed 'spot analysis', the researchers were able to demonstrate markedly reduced SMN levels in $CD33^{++}$ peripheral blood cells from patients with SMA. This biomarker test can be applied to small volumes (<1.5 ml) of blood and could potentially be used to monitor SMN levels — and, hence, treatment efficacy — in patients who are undergoing therapy for SMA.

ORIGINAL ARTICLE Otsuki, N. et al. A new biomarker candidate for spinal muscular atrophy: identification of a peripheral blood cell population capable of monitoring the level of survival motor neuron protein. *PLoS ONE* **13**, e0201764 (2018)

TRAUMATIC BRAIN INJURY

Traumatic brain injury induces transmissible tau pathology

A single severe traumatic brain injury (TBI) can result in the generation of self-propagating tau pathology, according to new research reported in *Brain*. Repetitive mild TBI has been linked to the tauopathy chronic traumatic encephalopathy (CTE), but until now, little attention has been paid to the long-term pathological effects of a single moderate or severe TBI event.

"Tau aggregates extracted from Alzheimer disease (AD) brains can trigger endogenous tau aggregation when injected into the mouse brain, indicating that AD-associated tau can acquire the ability to self-propagate, like the prion proteins that are responsible for Creutzfeldt–Jakob disease," explains prion expert Roberto Chiesa, who co-directed the research with Elisa Zanier, an expert in TBI. "We decided to investigate whether tau in the context of TBI also showed prion-like behaviour."

First, the researchers examined post-mortem brain tissue samples from patients who had survived for ≥1 year after a single moderate or severe TBI event. In contrast to brain tissue from age-matched controls without TBI, these samples showed extensive deposition of hyperphosphorylated tau (P-tau) — a pathological form of tau observed in conditions such as AD and CTE.

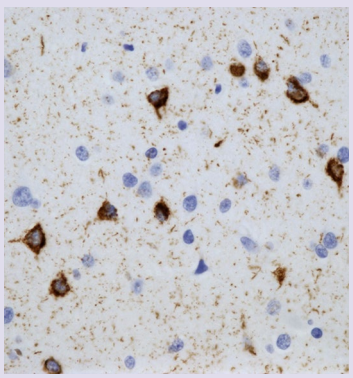
"In this case series, it was not possible to establish whether TBI accelerates a pre-existing age-related tau pathology or whether it triggers de novo tau deposition," says Zanier. "To address this point, we sought evidence of emerging and self-propagating tau pathology in wild-type mice subjected to severe TBI."

Three months after a single severe TBI in mice, Zanier and colleagues were able to detect P-tau deposits adjacent to the injury site.

NEURODEGENERATIVE DISEASE

*APOE*ε4* — a risk factor for TDP43 pathology?

The main genetic risk factor for Alzheimer disease (AD) pathology is also associated with TAR DNA-binding protein 43 (TDP43) proteinopathy, the main pathology in amyotrophic lateral sclerosis and frontotemporal dementia, new research has shown. A possible causal role for TDP43 pathology in hippocampal sclerosis was also identified.



Credit: A higher burden of TDP43 pathology (brown) was associated with *APOE*ε4*. Image courtesy of Alifiya Kapasi.

TDP43 proteinopathy frequently coexists with AD pathology and hippocampal sclerosis, but its relevance in these contexts is unclear. "We were intrigued by this coexistence, and aimed to investigate whether AD pathology and TDP43 proteinopathy share a genetic risk factor," explains Hyun-Sik Yang, lead author of the new study. "We focused on the *APOE*ε4* haplotype, which is the strongest genetic risk factor for AD pathology."

Yang and colleagues analysed data from 1,044 participants of the Religious Orders Study and Rush Memory Aging Project cohorts. They assessed the relationships between *APOE*ε4* status and brain pathology.

The analysis showed that the number of *APOE*ε4* alleles correlated positively with TDP43 pathology. This association was not fully explained