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SoSTART recruited 203 patients during 2 years in 61 sites, and APACHE-AF recruited 101 patients during 5 years in 16 sites. An international effort is therefore extremely important if clinicians want to solve this clinical dilemma. Hopefully, randomised controlled trials are underway in different countries and investigators have planned an individual patient data meta-analysis (PROSPERO 2021 CRD42021246133).

Finally, some insight was serendipitously gained in 2021 into sporadic cavernomas. Until recently, the genetics of sporadic cerebral cavernous malformations (CCMs) were poorly understood. While they were studying meningiomas through a genetically modified mouse model (PIK3CA mutation), Peyre and colleagues unexpectedly observed typical CCMs that prompted them to investigate the possible involvement of this mutation in sporadic human CCMs.6 In a series of 88 surgically resected sporadic CCMs, the authors identified that 39% of lesions had PIK3CA somatic mutations. Of note, CCM genesis could depend on pericytes rather than on endothelial cells as previously believed. These data suggest that pharmacological targeted treatment (such as PIK3CA inhibitors that have shown promising results in oncology) could be the future of CCM management.

The stroke field is evolving year by year and 2021 was no exception. Thanks to the tremendous stroke community around the world, this collective momentum will continue for the benefit of patients.

CC is on a steering committee for Biogen (CHARM study) and Bristol Myers Squibb (AXIOMATIC study), has received speaker fees from Boehringer-Ingelheim, is on an advisory board (minor stroke and antiplatelet agents) for AstraZeneca, and is the principal investigator for the A3ICH study (funded by French Ministry of Health). LP declares no competing interests.

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## 2021 marks a new era for Alzheimer's therapeutics



2021 was a year of both hope and despair for the dementia field. The COVID-19 pandemic had a particularly detrimental effect on older populations and patients with dementia, with an enormous death toll across the world. Yet, despite the COVID-19 pandemic disrupting both basic and patient-oriented research, the dementia field moved forward, with substantial advances from Alzheimer's disease research.

After considerable controversy, aducanumab became the first disease-modifying therapy targeting amyloid  $\beta$  to get approval through an accelerated process by the US Food & Drug Administration.¹ Debates on aducanumab's approval centred around disease modification through the clearance of amyloid  $\beta$  without a tangible clinical response, setting a precedent for the approval of other disease-modifying therapies on the basis of biomarker response. An important consequence of this approval was that it ignited momentum for developing guidelines to identify patients who could be the best candidates for

disease-modifying therapies targeting amyloid  $\beta$ , and best practices to safely treat and monitor them. Another promising development came from a phase 2 trial of donanemab in early symptomatic Alzheimer's disease. Donanemab reduced brain amyloid  $\beta$  and resulted in a better composite score for cognition and an increased ability to perform activities of daily living compared with placebo at 76 weeks. The change from baseline in the Integrated Alzheimer's Disease Rating Scale score at 76 weeks was -6.86 with donanemab and -10.06 with placebo (difference of 3.20; 95% CI 0.12–6.27; p=0.04).

Although therapy targeting amyloid  $\beta$  was in the spotlight, advancements also occurred in therapies targeting tau. The ADAMANT phase 2 study evaluated the safety, tolerability, immunogenicity, clinical efficacy, and biomarker response of the active tau vaccine AADvac1 in patients with mild Alzheimer's disease dementia. The safety profile was excellent and more than 98% of the vaccinated cohort elicited an antibody response. A clinical

effect was not shown; however, a third of the participants were tau-biomarker negative and did not have the target pathology. A reduction of CSF tau phosphorylated at threonine 217 (p-tau217) levels was observed in the treatment group compared with the placebo group, which was modulated by baseline p-tau217 levels, with those having higher p-tau217 at baseline responding better.<sup>4</sup>

After decades of research and development of biomarkers in the Alzheimer's disease field, biomarkers are now having a substantial impact on the development of disease-modifying therapies.5 Biomarkers were central to the approval process of aducanumab, and are being used in other phase 2 studies for patient selection and assessment of target engagement and treatment efficacy. Although PET imaging of amyloid β and tau were the most commonly used biomarkers in clinical trials, the crucical need for an accessible and reliable biomarker for clinical trials targeting diverse populations was also highlighted this year. The use of blood-based biomarkers was tested against molecular imaging findings and clinical and pathological diagnosis. Both plasma p-tau217 and p-tau181 had an excellent diagnostic performance in differentiating patients with Alzheimer's disease dementia from other neurodegenerative disorders.<sup>6</sup> In a cohort from the Swedish BioFINDER study, p-tau217 showed stronger correlations with amyloid-β and tau PET than other p-tau variants, as well as higher accuracy in separating Alzheimer's disease dementia from other dementias.7

In 2021, molecular imaging biomarkers also contributed to our understanding of disease mechanisms associated with microglial activation and tau spreading. A study of microglial activation measured with [ $^{11}\text{C}$ ]PBR28 PET along with tau and amyloid- $\beta$  PET showed that microglial activation and tau accumulation spatially propagate in parallel, following brain circuits and staging of neurofibrillary tangle tau pathology. Furthermore, findings from all three ligands indicated that amyloid  $\beta$  potentiates the effects of microglial activation on tau spreading.  $^8$ 

An important discovery was on the role of genetic variants of APOE on tau pathology and neurodegeneration. Investigations into neuronal APOE expression levels and selective neuronal vulnerability in Alzheimer's disease, by elimination or over-expression of neuronal APOE, identified a causal relationship among APOE

expression, neuronal MHC-I expression, tau pathology, and neurodegeneration, suggesting a mechanism linking neuronal APOE expression to MHC-I expression and, subsequently, to tau pathology and selective neurodegeneration.<sup>9</sup> Another study investigated the APOE3-Val236Glu (APOE3-Jacksonville) variant that is protective against Alzheimer's disease dementia. The APOE3-Jacksonville variant was found to reduce APOE aggregation and enhance lipidation, which has important implications in the design of APOE-targeted therapies.<sup>10</sup>

Finally, in the fields of Lewy body dementia, frontotemporal dementia, and vascular cognitive impairment, multisite consortia across the world were building on the findings of the Alzheimer's Disease Neuroimaging Initiative. Biomarker investigations into the prodromal and preclinical stages of these disorders and their overlap with Alzheimer's disease pathology were the highlights, and prepared the field for the potential development of individualised combination therapies that address each one of the proteinopathies, including  $\alpha$ -synuclein and TDP-43 in addition to amyloid  $\beta$  and tau, and cerebrovascular disease processes.

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