see whether neurologists start using cilostazol for stroke prevention in Japan, and more widely in Asia, where the global bulk of strokes occur, and eventually in the rest of the world.

Michael D Hill, Oscar R Benavente
Department of Clinical Neurosciences and Hotchkiss Brain Institute, University of Calgary and Foothills Medical Centre, Calgary, AB T2N4N1, Canada (MDH); and Vancouver Stroke Programme, University of British Columbia and Vancouver General Hospital, Vancouver, BC, Canada
michael.hill@ucalgary.ca

MDH reports personal fees from Merck, non-financial support from Hoffmann-La Roche Canada, grants from Covidien, Boehringer-Ingleheim, Stryker, Medtronic, and NoNO, outside the submitted work. MDH also has a patent Systems and Methods for Assisting in Decision-Making and Triaging for Acute Stroke Patients and owns stocks in Calgary Scientific, a company that focuses on medical imaging software. MDH is a director of the Canadian Federation of Neurological Sciences, a not-for-profit group, and has received grant support from Alberta Innovates Health Solutions, CIHR, the Heart and Stroke Foundation of Canada, and the National Institutes of Neurological Disorders and Stroke. ORB declares no competing interests.

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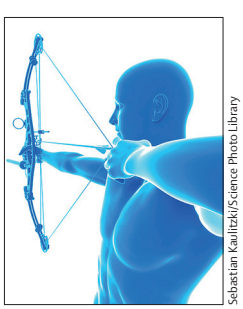
A new step towards targeting tau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See **Articles** page 549

Progressive supranuclear palsy is a rare neurodegenerative disease characterised by an axial parkinsonian syndrome, early falls, supranuclear gaze palsy, and frontal cognitive impairment.[1] In these patients, the response to levodopa is poor, and the disease rapidly leads to severe disability and death. Neuropathology shows aggregates of four microtubule-binding-domain-repeat (4R) tau in both neuronal and glial cells, and therefore immunotherapies targeting tau have been proposed as a potential treatment for the disease.

In *The Lancet Neurology*, Adam Boxer and colleagues[2] report the results of a randomised, double-blind, placebo-controlled, multiple ascending dose phase 1b trial, to investigate the safety and tolerability of BIIB092, a humanised monoclonal antibody targeting tau at its N-terminus, in patients with progressive supranuclear palsy. The primary endpoint was safety and secondary endpoints were pharmacokinetics and pharmacodynamics. 48 patients were randomly assigned to receive placebo or BIIB092 at 150 mg, 700 mg, or 2100 mg administered intravenously every 4 weeks for a total of 57 days. The treatment was well tolerated. Serious adverse events were reported in three patients treated with the highest dose of BIIB092, but none was considered related to the study drug, all were resolved, and no deaths were reported. BIIB092 concentrations in serum and CSF increased in a dose-dependent manner, with a CSF-to-serum ratio of 0·3% to 0·5%. The CSF concentration of unbound N-terminal tau was reduced by between 90% and 96% in patients treated with BIIB092. No changes were detected in the concentrations of total tau or phosphorylated tau. No significant change was observed in either clinical or neuroimaging exploratory endpoints.

These results are the first evidence of target engagement in CSF of anti-tau immunotherapy in patients with progressive supranuclear palsy, confirming previous results in healthy volunteers.[3] Demonstrating target engagement is an important step for drug development. Over the past decade, three large clinical trials done in individuals with progressive supranuclear palsy did not demonstrate clinical efficacy.[4–6] Because none of these trials provided evidence of a pharmacodynamic effect, the question remains as to whether

the negative outcomes were related to erroneous targeting or to target engagement failure. This study clearly demonstrates that BIIB092 crossed the blood–brain barrier and recognised N-terminal tau in the CSF. To establish whether the antibody reached the interstitial and cellular compartments, other biomarkers would be needed, such as tau PET tracers, currently under development. Target engagement does not, however, systematically lead to efficacy. A good example comes from research done in patients with Alzheimer's disease, in whom anti-amyloid therapy has not shown clinical efficacy despite evidence of target engagement on amyloid PET imaging. A clinical trial sufficiently powered to demonstrate clinical efficacy of BIIB092 in progressive supranuclear palsy is currently ongoing (NCT02658916).

An important observation from the study by Boxer and colleagues is the absence of changes in the concentration of total or phosphorylated tau in CSF. The authors suggest that the N-terminal tau bound to the antibody remains in the CSF, the N-terminal epitope being masked by the antibody used in the investigation, but not the tau mid-domain epitope used to measure total tau. However, truncated tau fragments are usually found in the CSF,[7] most of them containing the mid-region of tau but not always the N-terminus of the protein. This observation might also explain the target engagement without decreases in total tau. Whether tau concentration in CSF is a relevant marker in progressive supranuclear palsy remains to be confirmed. Low concentrations of tau protein are present in the CSF in healthy people. Tau concentration increases in individuals with Alzheimer's disease, but remains low in individuals with progressive supranuclear palsy, often lower than concentrations seen in healthy individuals. The reasons for this are unclear but some have suggested that amyloid pathology might promote secretion of tau in Alzheimer's disease;[7] in progressive supranuclear palsy, aggregation of tau in some areas of the brain without amyloid pathology[8] might explain the low concentration in CSF.

These results might have implications for other tauopathies. Tauopathies are distinguished on the basis of the composition of tau isoforms aggregated in the brain: Pick's disease is a 3R tauopathy; 4R tauopathies include progressive supranuclear palsy, corticobasal degeneration, and argyrophilic grain disease; and Alzheimer's disease presents as a mixed 3R and 4R tauopathy. Targeting the N-terminus of tau is attractive, particularly in Alzheimer's disease, because N-terminal fragments of tau have been detected in the CSF of individuals with Alzheimer's disease, and these fragments have been shown to increase β-amyloid production, further perpetuating the destructive cycle; studies in animal models have shown promising effects with N-terminus targeting of tau. This strategy is currently being investigated in patients with Alzheimer's disease (NCT03352557). However, the majority of tau in the Alzheimer's disease brain is truncated, mostly at the N-terminus.[9] Therefore, targeting the mid-region of tau might be an alternative strategy—a strategy that has shown some efficacy in animal models.[10] Ongoing clinical trials of antibodies and vaccine strategies targeting different species of tau in progressive supranuclear palsy, Alzheimer's disease, and other tauopathies will hopefully provide a clearer picture of the efficacy of anti-tau therapies.

Jean-Christophe Corvol, Luc Buée
Sorbonne Université, Assistance Publique Hôpitaux de Paris, Inserm, CNRS, Institut du Cerveau et de la Moelle, Department of Neurology, Hôpital Pitié-Salpêtrière, 75013 Paris, France (J-CC); and Université Lille, Inserm, CHU-Lille, LabEx DISTALZ, Lille Neuroscience & Cognition, Team Alzheimer & Tauopathies, Lille, France (LB)
jean-christophe.corvol@aphp.fr

J-CC reports grants from Sanofi and personal fees from Ever Pharma, Biogen, Air Liquide, BrainEver, Theranexus, Denali, and Alzprotect, outside of the submitted work. LB reports grants from UCB BioPharma, outside of the submitted work. LB also has two patents pending, titled "Method of treatment of tauopathy disorders by targeting new tau species" (EP19305369.1; March 25, 2019) and "New anti-tau single domain antibody" (EP18306684.4; Dec 13, 2018).

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