trial to identify patients who are most likely to benefit,[7,8] as noted by the authors.

What lessons might DARS offer for the design of future stroke rehabilitation drug trials? Experience-based therapy needs to be of sufficient intensity to interact with the tested drug and structured in a way that is synergistic with the drug's mechanisms of action. It is unlikely that a single drug will enhance recovery for all patients, and biomarkers could help to identify subsets of patients who are more likely to benefit. Testing rehabilitation drugs on a scale that allows for high treatment fidelity and sensitive outcome measures will produce more certain conclusions. Stroke recovery and rehabilitation are highly heterogeneous processes and are more likely to be improved by precision medicine than herd medicine.

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The uncertain role for phosphodiesterase inhibitors in stroke prevention

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Cilostazol has been an approved drug for the treatment of intermittent claudication in North America and Japan for more than 20 years, but not for stroke. Cilostazol is an oral phosphodiesterase (PDE) inhibitor, similar in mechanism of action to dipyridamole. Key pharmacological differences are that cilostazol inhibits PDE-3 with greater effect on intracellular cyclic-AMP concentrations and lesser effect on cyclic-GMP than dipyridamole. Dipyridamole inhibits PDE-5, which has a dominant effect on increasing intracellular cyclic-GMP concentrations; cyclic-GMP then inhibits PDE-3. Cilostazol is also an adenosine reuptake inhibitor that further increases intracellular cyclic-AMP and potentiates its action. In vascular smooth muscle, cilostazol results in vasodilation, has a 10 h half life, is primarily excreted renally, and its metabolism is influenced by cytochrome P450 enzyme variants (CYP3A4 and CYP2C19), the same as clopidogrel.[1,2]

Previous studies with cilostazol for stroke prevention have been completed. From 1992 to 1996, 1085 patients from Japan were enrolled in a double-blind study (the CSPS-1 trial)[3], and randomised to cilostazol or placebo, with a significant benefit accruing to cilostazol for stroke prevention. A pilot study enrolling 720 patients in China showed no difference in stroke recurrence between aspirin versus cilostazol as a single antiplatelet therapy.[4] A second study (CSPS-2 trial),[5] that enrolled 2757 patients in Japan, compared cilostazol 100 mg twice per day with aspirin 81 mg once per day in a non-inferiority design.[5] The study yielded borderline results; the annual rate of recurrent stroke was 2·8% in patients randomly allocated to cilostazol and 3·7% in those allocated to aspirin (HR 0·74, 95% CI 0·56–0·98), meeting the criteria for non-inferiority. There are parallels with findings from the trials of dipyridamole for stroke prevention, the ESPS-1,[6] ESPS-2,[7] and ESPRIT[8] trials, all of which initially suggested benefit for dipyridamole, despite design or execution concerns. The results of the PROFESS trial,[9] that enrolled 20 232 patients, confirmed that dipyridamole was not non-inferior and had similar outcome rates to clopidogrel alone.[9]

The Cilostazol Stroke Prevention Study for Antiplatelet Combination (CSPS.com) by Toyoda and colleagues,[10]

reported in this issue of *The Lancet Neurology*, describes a randomised controlled trial done entirely in Japan to assess cilostazol as an adjunctive therapy to aspirin or clopidogrel. Patients with non-cardioembolic ischaemic stroke, confirmed by MRI, were enrolled 8–180 days after stroke onset and randomly allocated to receive either monotherapy with oral aspirin (81 or 100 mg, once per day) or clopidogrel (50 or 75 mg, once per day) alone, or a combination of cilostazol (100 mg, twice per day) with aspirin or clopidogrel. All patients had to have two or more common stroke risk factors (eg, hypertension, diabetes, age ≥65 years, peripheral artery disease, chronic kidney disease, ischaemic heart disease, current smoker, or a past ischaemic stroke excluding the index event) or had to have proven atherosclerosis, defined as 50% or more stenosis of an extracranial cervical or intracranial artery. Although the evident goal of the risk factor criteria was to include patients with confirmed neurovascular atherosclerosis, 90% of patients had two or more risk factors, 29% had intracranial disease, and 14% had extracranial cervical artery atherosclerosis. Thus, a small number of patients had proven neurovascular atherosclerosis.

The reported effect size on the primary outcome of recurrent stroke was both rather high and occurred relatively fast, with a halving of the risk (4·5% per annum to 2·2% per annum) at a median follow-up time of only 1·4 years (hazard ratio 0·49, 95% CI 0·31–0·76, p=0·0010). There was no increase in haemorrhage (intracranial or systemic), no effect on myocardial infarction, and no effect on mortality. As a measure of impact, we do not know how disabling, and therefore how important, the recurrent strokes were. The stroke prevention effect was not modified by baseline factors. However, examination of subgroups leads to novel hypotheses to be tested. For example, the effect of cilostazol was less among patients without hypertension, those with chronic kidney disease, and those with extracranial cervical artery atherosclerosis. Are these results spurious or real? Perhaps the mild blood pressure lowering effect of cilostazol is relevant.

The trial[10] was an open-label study; all participants knew which drug they were taking. Three times more patients in the cilostazol group (9·8%) discontinued the study drug or withdrew consent (7·8%) than discontinued (3·5%) or withdraw consent (1·5%) in the control group. This finding might primarily have been caused by the headaches induced by cilostazol. The study[10] was halted prematurely for slow recruitment and funding reasons; the investigators enrolled 1884 of a planned cohort of 4000 participants. It remains possible that the study was halted at a random high point in effect size, as is always possible with premature study termination. 292 sites were involved, meaning that on average each site enrolled only six or seven patients. Knowing that the distribution of enrolment tends to have a few high-enrolling sites and many sites that enrol one or two patients, and knowing that the study used a permuted blocks randomisation process, imbalances in randomisation within strata are predicted to be very probable. It is also interesting that the CHANCE trial,[11] which showed that dual antiplatelet therapy with aspirin and clopidogrel for 21 days acutely after transient ischaemic attack or minor stroke reduced the risk of early recurrent stroke dramatically, and which was published when the CSPS.com trial[10] was beginning, had little effect on practice in Japan and did not make the CSPS.com trial unethical because clopidogrel was not approved for acute transient ischaemic attack or minor stroke treatment and the findings did not have substantial uptake by Japanese neurologists.

It is difficult to make a prediction of the impact on stroke prevention strategies from the CSPS.com study. It is certain that regulatory approval in North America will require another trial to be done in a double-blind fashion with a longer follow-up period. Yet, the CSPS.com trial was innovative in the way it made use of diagnostic imaging to define the patient population. The goal of identifying patients with atherosclerosis with confirmed stroke, and then targeting their atherosclerotic disease is meritorious. The SPS3 trial[12] was the first medical trial to use imaging to target a specific patient population with subcortical small stroke for long-term stroke prevention. A post-hoc analysis of the SOCRATES study[13] supported this approach, and newer antithrombotic studies are also targeting this paradigm of using imaging to select a specific target stroke mechanism and therefore a specific patient population for stroke prevention therapies. A considerable body of preclinical and now tantalising clinical evidence support that cilostazol is a useful agent for stroke prevention. Overall, however, the evidence for the efficacy of PDE inhibitors for stroke prevention is marred by weaknesses in study design and study execution. It would be interesting to

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.

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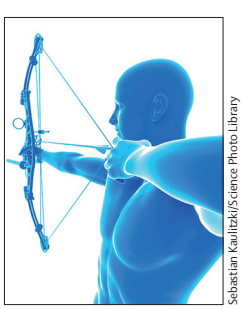
A new step towards targeting tau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Progressive supranuclear palsy is a rare neurodegenerative disease characterised by an axial parkinsonian syndrome, early falls, supranuclear gaze palsy, and frontal cognitive impairment.[1] In these patients, the response 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