body myositis[4] or sarcopenia,[5] bimagrumab led to increased performance in 6MWD, which suggests some functional improvement of the leg muscles; however, in the previous inclusion body myositis study,[4] quantitative measures of muscle strength remained unchanged. Second, muscle regeneration and muscle growth are largely impaired in patients with inclusion body myositis.[6] Inflammatory cell stress is a major component of the pathology of inclusion body myositis and is thought to directly contribute to muscle weakness.[1,7] Therefore, addressing muscle growth without targeting cell stress and other factors that lead to muscle damage is unlikely to provide sustained muscle growth and augmented muscle strength.[1,7] Bimagrumab could serve as an add-on component in future trials that aim to diminish muscle cell stress in patients with inclusion body myositis or other neuromuscular disorders. Finally, the 6MWD has been used as an endpoint in studies of myopathies and various other diseases, including cancer, pulmonary dysfunction, and heart disease.[8] Many factors other than leg muscle function are relevant for walking performance, including breathing, circulation, and physical fitness at the time of the assessment. If a patient has fatigue, the 6MWD can indicate an impairment, compared with test results after rest. Other primary endpoints—eg, the inclusion body myositis functional rating scale or the sIFA score—might be more reliable and, in addition to walking ability, capture several items of daily life that are usually affected in patients with inclusion body myositis.[9]

The RESILIENT study is valuable for our understanding of the pathology of inclusion body myositis and disease progression over the course of a year. Modulation of the myostatin system in neuromuscular diseases will continue to be investigated, but will not be without hurdles. In that respect, bimagrumab seemed to be safe and well tolerated in the RESILIENT study.[2] For patients with inclusion body myositis, other drugs are awaited—eg, arimoclomol and sirolimus, two drugs that are available orally. Arimoclomol is currently under investigation in clinical trials of inclusion body myositis and amyotrophic lateral sclerosis.[1] This drug's main mechanism of action is enhancement of heat shock protein function that protects cells from stress. Sirolimus is a well established immunosuppressant in transplantation surgery. This drug acts via suppression of the mammalian target of rapamycin and reduces T-cell proliferation. The effect of sirolimus on macroautophagic activity—a central element of muscle degenerative cascades around amyloid precurser protein and β-amyloid—led to initiation of a phase 2 trial in inclusion body myositis, which showed promising results; a larger trial is planned.[1,7] Along with these and similar approaches, blockade of the myostatin pathway could serve as a potentially useful add-on intervention in future studies. The number of past and ongoing clinical trials in inclusion body myositis provides hope that a beneficial treatment can be identified in the future.

Jens Schmidt
Department of Neurology, Muscle Immunobiology Group, Neuromuscular Center, University Medical Center Göttingen, 37075 Göttingen, Germany
j.schmidt@gmx.org

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Lessons from an unsuccessful therapeutic trial

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The development of a new medical treatment can be a herculean task. To be proven efficacious in a clinical trial, not only must a treatment effectively engage its target, but also investigators must choose the correct outcome as a metric of clinical effect, select an appropriate dose for testing, and enroll a suitable patient population,

among many other important variables. Negative results are an important—albeit frustrating—step in the process of drug discovery.

Opicinumab is a humanised monoclonal antibody that targets LINGO-1, a transmembrane protein with purported importance in the biology of oligodendrocyte differentiation, among other effects in the CNS. In *The Lancet Neurology*, Diego Cadavid and colleagues report findings of the SYNERGY trial,[1] a phase 2, randomised, double-blind trial comparing four doses of opicinumab (ranging from 3 mg/kg to 100 mg/kg) with placebo for the treatment of patients with relapsing forms of multiple sclerosis. The drug did not meet the prespecified primary outcome of confirmed improvement in neurophysical function, cognitive function, or both, over 72 weeks of treatment, with a linear dose-response not recorded (p=0·89). What can we learn from this trial?

The SYNERGY investigators recruited an adequate number of participants (n=419). However, several factors might have contributed to the trial's negative outcome. First, the multicomponent primary outcome measure was complex and has not been previously validated. It combined several existing disability measurements (ie, the Expanded Disability Status Scale, the Timed 25-Foot Walk, the Nine-Hole Peg Test, and the 3 s Paced Auditory Serial Addition Test) to assess improvement in function. An expectation was that remyelination—if achieved—would restore neurological function and not merely protect against future neurological decline from secondary axonal loss. Another assumption was that the function restored would be measurable using the metrics selected. On the basis of the success of the ReBUILD trial, which assessed the effects of clemastine (an antimuscarinic compound) on patients with multiple sclerosis or chronic optic neuropathy,[2] it is reasonable to assume that remyelination will associate with functional recovery on electrophysiological measures, and that this improvement will lead to better neurological function. However, among the metrics assessed in SYNERGY, none has proven sensitive for detection of the type of functional recovery one would expect with a remyelinating drug. The degree of anticipated improvement must be realistic enough to be achievable, yet robust enough to indicate true improvement rather than measurement of noise. It is noteworthy that the negative outcome of the SYNERGY trial does not mean that the metric tested does not work; it could simply be that the drug is not up to the task. The attempt by Cadavid and colleagues to develop new metrics is responsive to the needs of the field.

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Second, successful validation of an outcome depends on an efficacious treatment. There are good reasons to be cautious when considering the likelihood that opicinumab would serve as an effective remyelinating agent. Antibody-based approaches are counterintuitive when a cellular target resides in the CNS, because less than 0·1% of antibodies cross the blood–brain barrier.[3] Evidence suggests that LINGO-1 inhibits differentiation of the ready pool of endogenous oligodendrocyte precursor cells that constitute up to 8% of the cells of the adult CNS,[4] but to get to these cells the drug must transit from the circulation into the CNS. LINGO-1 is also expressed in neurons and astrocytes,[5] and this absence of cellular specificity means that off-target effects should be anticipated, and undermines an approach that pursues molecular specificity via use of an antibody. Furthermore, LINGO-1 as a therapeutic target deserves scrutiny. Inactivation of LINGO-1 either directly or via a dominant negative virus enhances differentiation of oligodendrocyte precursor cells.[6] However, LINGO-1 was first identified as a co-receptor for a neurite outgrowth inhibitor (NOGO) on neurons and was initially thought to be important for limiting axonal outgrowth.[7] Moreover, potential therapeutic monoclonal antibodies against LINGO-1 have not been tested to confirm the anticipated absence of biological effect in a LINGO-1 knockout model. In addition, conditional knockout models to ascertain the cellular specificity of LINGO-1 have not been described. It is therefore possible that antibody-based LINGO-1 antagonism is not capable of achieving remyelination in multiple sclerosis.

It is tempting to try to salvage a negative trial outcome by looking for possible therapeutic success in a subset of patients. In the SYNERGY trial, based on findings of a prespecified univariate subgroup analysis, Cadavid and colleagues identified a post-hoc subpopulation in which moderate doses of opicinumab (10 mg/kg) might be efficacious.[1] In the RENEW trial,[8] opicinumab at a dose of 100 mg/kg was administered to patients with acute optic neuritis. Similar to the SYNERGY trial, the primary endpoint of RENEW was not reached, but a post-hoc per-protocol analysis suggested possible efficacy. Post-hoc results that show marginal

significance, particularly those that do not have a clear and unambiguous biological rationale, should be viewed with caution.[9]

The presumption in dose-finding is that a specific threshold dose will show optimum efficacy, with fewer side-effects at lower doses.[10] The usual reason to assess multiple doses is to find the dose with the highest potential efficacy but that is still within an acceptable range regarding side-effects. Dose–response curves are generally sigmoidal, but U-shaped curves have also been reported, whereby the therapeutic effect at one dose is attenuated at a higher dose. However, evidence for such a dose–response would need to be robust, and a dose–response in a narrow therapeutic range raises concerns about the actual clinical application of such treatment. The pharmacokinetics of a drug generally means that target tissues are not exposed to one static dose of drug and exposure varies across patients.

The importance of oligodendrocyte precursor cell differentiation as a means of achieving remyelination remains very relevant, despite the intrinsic limitations of opicinumab and its therapeutic failure in relapsing multiple sclerosis[1] and acute optic neuritis.[8] The negative findings are likely to be a reflection of the antibody-based approach or that LINGO-1 might not be an appropriate biological target to achieve remyelination. Although it might be impossible to know exactly why the SYNERGY trial was unsuccessful, the field will benefit from recognising that the therapeutic approach investigated here is not a path forward. Regardless, remyelination remains a promising tactic for preventing disability and restoring function for patients with multiple sclerosis.

Ari J Green
University of California at San Francisco (UCSF) Weill Institute for Neurosciences, Department of Neurology, Division of Neuroimmunology and Glial Biology, San Francisco, CA 94143, USA; and UCSF Department of Ophthalmology, Division of Neuro-Ophthalmology, San Francisco, CA, USA
agreen@ucsf.edu

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Blood pressure in intracerebral haemorrhage: which variables matter?

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Blood pressure reduction in patients with acute intracerebral haemorrhage is an important, unresolved issue in stroke management. Two large clinical trials have shown inconsistent results, but are now combined for further analyses. The main phase of the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT2) with 2839 patients found that intensive systolic blood pressure reduction (target <140 mm Hg within 1 h, cessation of treatment at <130 mm Hg) within 6 h of onset of intracerebral haemorrhage improved functional recovery on a number of secondary outcomes, although the primary outcome (death or major disability at 90 days post-randomisation) was not significant. By contrast, the second Antihypertensive Treatment of Acute Cerebral Hemorrhage Trial (ATACH-II) with 1000 patients used a more intensive strategy (target 110–139 mm Hg