The Nerve to Give BACE Inhibitors a Second Chance?

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Inhibitors of β -site amyloid precursor protein (APP)-cleaving enzyme (BACE) were once a major focus of the pharmaceutical industry because of their prospects for treating Alzheimer's disease (AD) [1]. Following the discovery of BACE1 in 1999 [2–5] as an aspartyl protease that cleaves APP to generate aggregation-prone fragments, the potential to develop BACE inhibitors to treat AD was immediately apparent, and many pharmacologic inhibitors were engineered [6]. However, after 20 years and repeated failures in costly late-stage pivotal trials, BACE inhibition as a therapeutic strategy for AD is all but abandoned [7]. Among the problems for BACE inhibitors appears to be that BACE1 is a promiscuous protease, with over 60 substrates now recognized [8]. This promiscuity leads to significant potential for unwanted side effects due to altered cleavage of proteins other than APP, several of which regulate synaptic function and may have been responsible for the unexpected worsening of cognition seen in BACE1 inhibitor AD trials [9]. However, in theory, the existence of additional BACE1 substrates provides opportunity to repurpose BACE inhibitors for diseases other than AD.

Not long after its discovery as an APP protease, BACE1 was also found to cleave type III neuregulin 1, which is critical for axonal-Schwann cell communication during peripheral nerve development, and BACE1 knockout mice demonstrate developmental phenotypes of hypomyelination and abnormal axonal sorting in peripheral nerves [10, 11]. In addition, BACE1-mediated cleavage of APP was reported to induce axonal degeneration via a death receptor 6 (DR6) and caspase 6 dependent mechanism [12], suggesting multiple roles for BACE1 in mediating peripheral nerve development and degeneration.

Therefore, in 2011, the group led by Drs. Farah and Griffin investigated whether lack of BACE1 altered axonal

degeneration and found that while BACE1 knockout axons degenerated normally after axotomy or chemically induced neuropathy, they unexpectedly found accelerated axonal regeneration and enhanced reinnervation of neuromuscular junctions [13]. Additionally, they later showed that overexpression of BACE1 inhibited peripheral nerve regeneration [14]. This led to the proposal that a subset of BACE1 substrates in neurons, macrophages, and Schwann cells have a net negative effect on peripheral axon regeneration, and suggested that BACE1 inhibition could be therapeutically useful to treat nerve injury by promoting a growth permissive microenvironment.

In the current issue of *Neurotherapeutics*, Tallon et al. build on their previous work and demonstrate that pharmacologic BACE inhibition can improve axonal regeneration in an axonal crush model, and enhance terminal sprouting in a partial nerve lesion model [15]. They chose a transient dosing paradigm to address the issue of decreased remyelination predicted from blocking type III neuregulin signaling. While peripheral axons have the capacity to regenerate, the process is generally incomplete and inefficient, and target tissues undergo atrophy and death, which precludes functional recovery [16, 17]. Therefore, agents that improve regeneration after peripheral nerve injury are an area of unmet medical need.

In addition to a peripheral nerve injury model, Tallon et al. treated SOD1^{G93A} transgenic mice, a model of amyotrophic lateral sclerosis (ALS), with a BACE1 inhibitor and observed that while there was transient benefit in functional innervation, this effect disappeared over time. This finding mirrors the results of other attempts at using axonal protective therapies in preclinical models of motor neuron disease [18–20], where axonal protective therapies provided only transient benefit early in disease. This leaves the prospects of BACE1 inhibitors in ALS less certain, since it is unclear whether transient axonal protection would have clinical benefit for patients with the disease.

While the authors were able to show that cleavage of the BACE1 substrate Close Homolog of L1 (CHL1) is diminished in SOD1^{G93A} transgenic mice, a key question remains unanswered—what is/are the substrate(s) that mediate the

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promotion of a growth permissive environment by BACE1 inhibition in peripheral nerves? A better understanding of the mechanism could lead to development of more substrate focused therapeutic agents to improve peripheral nerve regeneration. Regardless, significant challenges remain in further advancement toward clinical application for peripheral nerve diseases. The variability of injury mechanism and recovery after peripheral nerve trauma in general makes it difficult to design a trial to properly demonstrate clinical benefit of axonal protective agents [21]. Likewise, long-term treatment may be problematic due to unwanted side effects from inhibition of a variety of BACE1 substrates in both the central and peripheral nervous system, limiting application for chronic acquired or inherited peripheral neuropathies. However, several of these (e.g., chemotherapy-induced neuropathy, Charcot-Marie-Tooth disease, etc.) have a more tractable path in terms of natural history data and outcomes measures for clinical trial design, and if BACE inhibition can find the right balance to generate a growth permissive environment for peripheral axons, then perhaps someone will have the nerve to give BACE1 inhibitors a second chance.

Required Author Forms [Disclosure forms](#) provided by the authors are available with the online version of this article.

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