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Review

# Advancing neurotrophic factors as treatments for age-related neurodegenerative diseases: developing and demonstrating "clinical proof-of-concept" for AAV-neurturin (CERE-120) in Parkinson's disease

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**Abstract**

Neurotrophic factors have long shown promise as potential therapies for age-related neurodegenerative diseases. However, 20 years of largely disappointing clinical results have underscored the difficulties involved with safely and effectively delivering these proteins to targeted sites within the central nervous system. Recent progress establishes that gene transfer can now likely overcome the delivery issues plaguing the translation of neurotrophic factors. This may be best exemplified by adeno-associated virus serotype-2-neurturin (CERE-120), a viral-vector construct designed to deliver the neurotrophic factor, neurturin to degenerating nigrostriatal neurons in Parkinson's disease. Eighty Parkinson's subjects have been dosed with CERE-120 (some 7+ years ago), with long-term, targeted neurturin expression confirmed and no serious safety issues identified. A double-blind, controlled Phase 2a trial established clinical "proof-of-concept" via 19 of the 24 prescribed efficacy end points favoring CERE-120 at the 12-month protocol-prescribed time point and all but one favoring CERE-120 at the 18-month secondary time point ($p = 0.007$ and 0.001, respectively). Moreover, clinically meaningful benefit was seen with CERE-120 on several specific protocol-prescribed, pairwise, blinded, motor, and quality-of-life end points at 12 months, and an even greater number of end points at 18 months. Because the trial failed to meet the primary end point (Unified Parkinson's Disease Rating Scale motor-off, measured at 12 months), a revised multicenter Phase 1/2b protocol was designed to enhance the neurotrophic effects of CERE-120, using insight gained from the Phase 2a trial. This review summarizes the development of CERE-120 from its inception through establishing "clinical proof-of-concept" and beyond. The translational obstacles and issues confronted, and the strategies applied, are reviewed. This information should be informative to investigators interested in translational research and development for age-related and other neurodegenerative diseases.


*Keywords:* Parkinson's disease; Translational research; Neurodegenerative diseases; Neurotrophic factors; Neurturin; CERE-120; Therapeutic development; Clinical 'proof-of-concept'; Gene transfer; Gene therapy; Viral vectors; Protein delivery

## 1. Introduction

Neurotrophic factors offer one of the most compelling opportunities to significantly improve the treatment of serious age-related, neurological diseases such as Alzheimer's and Parkinson's, as well as Huntington's and amyotrophic lateral sclerosis. The therapeutic potential of neurotrophic factors to alleviate the symptoms and slow or even halt disease progression in neurodegenerative diseases, including Parkinson's disease (PD), is widely acknowledged (Apfel et al., 2000; Eriksdotter Jönhagen et al., 1998; Mufson et al., 1999; Seiger et al., 1993) and has been independently

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supported by research conducted by numerous laboratories around the world. A major translational advantage of neurotrophic factors is that they offer the opportunity to treat both the symptoms of a disease (thus improving clinical status) as well as its pathogenesis (thus delaying disease progression) without any prerequisite, deep insight into the etiology or specific pathogenic variables driving the disease process. An editorial written more than two decades ago, entitled "Neurotrophic factors: can the degenerating brain be induced to heal itself," helps illustrate the enthusiasm many of us have felt for a long time, excerpted here: "When one considers the history of neurology, the idea that one might be able to treat patients so that their brain cells might either withstand deadly perturbations or regenerate to a healthier, more functional state is truly revolutionary. Never before in the history of medical science could we imagine the means to induce damaged parts of the brain to heal" (Bartus, 1989a). While it was clearly too early to know whether neurotrophic factors might eventually live up to those early expectations, it would have been even more difficult for anyone to have known that after more than two decades of animal research and many clinical trials attempting to show efficacy in humans, their ability to treat human neurodegenerative diseases would continue to remain unfulfilled this long.

Neurotrophic factors are endogenous proteins that have consistently demonstrated that under conditions of neurodegeneration they are able to activate neuronal repair genes when supra-physiological (i.e., biopharmaceutical) levels are achieved. Induction of these repair genes routinely produces morphological and functional restoration of the degenerating neurons, significantly slowing further neurodegeneration and even protecting against cell death (Hefti et al., 1989). Thus, decades of research using numerous animal models argues that neurotrophic factors provide the opportunity to substantially improve neuronal vitality and function in human neurodegenerative diseases (thus potentially improving symptoms and extending the value of current pharmacotherapies), as well as to protect against further neurodegeneration (possibly slowing, halting, or even reversing disease progression).

An extremely important point for translational purposes is that neurotrophic factors appear to provide functional and morphological benefit to their responsive neurons, no matter how the neurons are damaged or impaired. Investigators have consistently shown benefit of neurotrophic factors against cutting and/or crushing axons, exposure to neurotoxins, free radical donors, inflammatory agents and other cytotoxic agents, genetic mutations, protein processing defects, and the effects of age. Thus, neurotrophic factors seem to represent a final common therapeutic pathway to achieve neuronal restoration and protection, likely providing potential benefit independent of which of many possible pathogenic cascade(s) are truly responsible for the disease and thus free of theoretical insight, assumptions, or uncertainties surrounding those issues. The potential therapeutic effects of neurotrophic factors seem to be "pathogenic neutral," which offers a major translational advantage, given the apparent complexity of most chronic neurodegenerative diseases as well as the uncertainty and controversy regarding which pathogenic variables are most important. Therefore, if one is able to identify a neuronal population whose degeneration and/or loss of function has been linked to the symptoms or pathogenesis of a disease, then the appropriate neurotrophic factor can likely provide restorative effects independent of a clear understanding of the pathogenesis involved. This rather unique characteristic of neurotrophic factors provides a significant, perhaps unprecedented opportunity to reduce risk in the development of "first in class" therapeutics for serious, unmet needs. This approach to treat neurodegenerative diseases leverages decades of cross-disciplinary research that collectively establishes "nonclinical proof-of-concept" for the potential benefit of neurotrophic factors when degeneration of a specific neuronal population is known to represent a key feature of a disease.

This scenario makes neurotrophic factors a compelling target for translational research and development (R&D). Moreover, the complex but powerful biology of neurotrophic factors suggests that if a significant reduction in clinical symptoms can be achieved, then a slowing of disease progression should also occur, simply because the same repair genes activated by the neurotrophic factor to improve symptoms should also produce healthier neurons that are better able to withstand the pathogenic variables responsible for disease progression. As many have noted in the past, this possibility of reversing and slowing disease progression represents the "Holy Grail" for neurological diseases and neurotrophic factors arguably provide the best opportunity to accomplish this in the foreseeable future.

The major reason neurotrophic factors have not lived up to their early promise centers around the long-standing translational obstacles that impeded safe and effective delivery. While an editorial written decades ago titled "Delivery to the brain: the problem lurking behind the problem" forewarned that a major translational stumbling block for neurotrophic factors might involve successful delivery to the brain (Bartus, 1989b), that problem has proven to be far more difficult than we had reason to believe at the time. Similarly, while no one can be certain that solving delivery issues will necessarily produce the anticipated clinical benefit, it has become increasingly accepted that unless the delivery problems are solved, reliable and meaningful clinical benefit will likely not be achieved.

Numerous clinical trials, testing many different neurotrophic factors in several different neurodegenerative diseases, have been conducted over the past 20 years (Apfel, 2002; Apfel et al., 1998, 2000; Eriksdotter Jönhagen et al., 1998; Gill et al., 2003; Lang et al., 2006; Marks et al., 2008; Miller et al., 1996; Nutt et al., 2003; Penn et al., 1997; Slevin et al., 2005; Tuszynski et al., 2005; Wellmer et al.,