The new wave of p75 neurotrophin receptor targeted therapies

Amanda M. Crooks, Rick B. Meeker*

Neurotrophins have been recognized for decades for their beneficial effects on growth, survival, and maintenance in the central nervous system, all of which suggest potential therapeutic utility. Although understanding and harnessing the activity of neurotrophins has proven difficult, the past several years have seen significant strides in the development of deliverable therapies that modulate neurotrophin activity (Shen et al., 2019; Yang et al., 2020; Xie et al., 2021). These recent studies have primarily focused on the multifunctional p75 neurotrophin receptor ($p75^{NTR}$) which is upregulated in central nervous system disease and injury, thus offering a unique target for intervention. Animal studies focusing on neurodegenerative diseases, infection and injury have all illustrated the potential benefit of $p75^{NTR}$ modulation, such as prevention of neural damage via restoration of calcium homeostasis, facilitation of pro-survival signaling, and reduction of inflammation. In addition, new studies have revealed important interactions of $p75^{NTR}$ with microtubule-associated protein, Tau, relevant to Alzheimer's disease (AD) pathogenesis, tauopathies, injury, and infection. Importantly, these investigational therapies have also been shown to be effectively deliverable as well as tolerable, with few side effects in animal models. Although the actions of $p75^{NTR}$ are complex and studies have only begun to reveal their potential utility, these new developments have paved the way for clinical trials of focused, modulatory interventions that have the potential to be broadly applicable in the treatment and prevention of central nervous system disease.

Neurotrophins and neurodegenerative diseases: Attempts to develop disease modifying treatments for neurodegenerative diseases have been largely unsuccessful. While there are many reasons for the lack of success, key deficiencies have been an incomplete understanding of the mechanisms surrounding onset and early progression of neurodegenerative diseases such as AD and the lack of biomarkers that can be used to identify patients in early stages of disease pathogenesis, where interventions have the potential to alter the disease course. Efforts to develop such treatments are ongoing and generally focus on protection of neurons, interference with the disease process or improvement/elimination of risk factors that facilitate disease. For example, treatments may block the neuronal effects of toxic factors such as viral proteins, eliminate formation of toxic entities such as oligomeric Aβ and Tau or reduce risk factors such as inflammation.

Due to their well-known neuroprotective properties, neurotrophins were among the first molecules investigated as therapeutic agents in the central nervous system. However, difficulties with compound stability, delivery to the central nervous system, and adverse effects impeded the path to clinical use for decades. The introduction of Cerebrolysin, a complex mixture of porcine brain-hydrolysate which includes neurotrophic factors, provided the first European approved clinical use of a therapy based, in part, on neurotrophic activity. Clinical trials showed superiority to placebo in improving cognitive ability in patients with AD (Gavrilova and Alvarez, 2020) and an orally available derivative, N-PEP-12, has been developed and used in initial clinical trials for ischemic stroke (Balea et al., 2020). Recent efforts focused on the treatment of neurodegenerative diseases, viral neuropathogenesis, and injury have begun to explore more specific strategies for modulation of neurotrophin receptor signaling and have resulted in the emergence of novel interventions designed to tap the enormous potential of neurotrophins for therapeutic purposes. This perspective highlights some of these recent developments with a focus on modulation of p75 neurotrophin receptor ($p75^{NTR}$) signaling.

The emerging role of $p75^{NTR}$ as a driver of neuropathogenesis: The relationship between neurotrophins and neurodegenerative diseases is best developed for AD, where the loss of cholinergic input from the basal forebrain to the cortex and hippocampus is closely linked to changes in nerve growth factor (NGF) signaling. A major turning point in our understanding of neurotrophin signaling was the discovery of opposing effects of mature versus pro-neurotrophins. The protective, pro-survival actions of mature neurotrophins at tropomyosin receptor kinase (Trk) A, B and C receptors contrasted strongly with the neurodegenerative, pro-apoptotic effects of the pro-neurotrophins at the $p75^{NTR}$. In AD as well as advanced age, the balance shifts from pro-survival NGF/TrkA signaling to favor the more inflammatory and degenerative state of high $p75^{NTR}$ expression and elevated pro-neurotrophins.

The balance of mature and pro-neurotrophin signaling also regulates immune function in a fashion that parallels the effects on neurons. Increased proNGF/$p75^{NTR}$ signaling in macrophages and microglia under various pathological conditions shifts the functional phenotype of these cells to promote inflammation (Xu et al., 2019) and the secretion of neurotoxic factors (Williams et al., 2016). Given the expanding evidence for inflammation as a contributing factor to disease onset and progression in AD (Heneka et al., 2015), HIV infection (Xie et al., 2021) and other neurodegenerative conditions, it is now clear that neurotrophin modulation may provide additional therapeutic benefits by controlling deleterious immune activity.

Evidence from many *in vitro* studies and animal models indicate that $p75^{NTR}$ expression increases from low/undetectable baseline levels during the very early stages of neural stress, coincident with the development of microglial activation (Xie et al., 2021). This early shift in neurotrophin receptors occurs before the development of disease specific markers of neurodegeneration, suggesting that intervention may have the potential to modify the course of the disease. The hypothesis that proNGF signaling via the $p75^{NTR}$ favors degenerative signaling and the potential for early disease modification have led to various novel efforts to develop therapies that regulate the actions of this receptor.

Efforts to develop therapies that target $p75^{NTR}$: Focused pharmacological approaches for the modulation of $p75^{NTR}$, summarized in **Additional Table 1**, have been at the forefront of many efforts to enhance the beneficial pro-survival, pro-repair actions of neurotrophins while preventing degenerative effects of pro-neurotrophin/$p75^{NTR}$ signaling. Two approaches in particular have illustrated how $p75^{NTR}$-based interventions have advanced toward clinical trials.

LM11A-31: LM11A-31 is a small non-peptide ligand with a molecular weight of 316.27 (dihydrochloride salt) designed to engage the $p75^{NTR}$ within the NGF loop1 binding domain as characterized by Massa, Longo and others in 2006. The ligand suppresses degenerative $p75^{NTR}$ signaling and facilitates pro-survival PI3K/Akt signaling by modulating the activity of $p75^{NTR}$ in a fashion that is neither a strict agonist or antagonist. The ability to modulate neurotrophin signaling may contribute to the favorable side effect profile by minimizing potential adverse effects of strong activation or suppression. *In vitro* studies modeling AD or viral neuropathogenesis showed that the compound provided neuroprotection at low nanomolar concentrations by suppressing early neurodegenerative processes such as calcium accumulation and cytoskeletal damage. Xie et al. (2021) recently published findings that point to a neuroprotective and anti-inflammatory action of LM11A-31 in an HIV infection model. In mice expressing the HIV gp120 envelope protein, an early age- and disease-related increase in $p75^{NTR}$ was paralleled by an accumulation of extracellular Tau aggregates in the hippocampus, similar to early stages of other neurodegenerative diseases such as AD. Treatment of the mice with LM11A-31 was effective in suppressing neurodegeneration and inflammation but not the hypophosphorylated Tau aggregates. The close relationship between $p75^{NTR}$ and Tau in these studies was unexpected but paralleled a growing number of observations suggesting novel interactions between these proteins early in the disease process. Work done by Manucat-Tan in 2019 demonstrated that $p75^{NTR}$ deletion reduced Tau hyperphosphorylation in pR5 mice expressing the Tau P301L mutation,

establishing a role for p75^{NTR} in Tau hyperphosphorylation (Manucat-Tan et al., 2019). Additionally, a 2020 study by Yang et al. in Tau P301S mutant mice showed that treatment with LM11A-31 inhibited Tau phosphorylation, acetylation, misfolding and accumulation of mutant Tau aggregates (Yang et al., 2020). The treatment also decreased synaptic degeneration, promoted pyramidal neuron neurite complexity, and improved hippocampal behavioral outcomes. The specific mechanisms by which LM11A-31 interacts with p75^{NTR} to offer protection are not completely understood but may be due, in part, to activation of the PI3K-Akt pathway and inhibition of enzymes, such as GSK-3β, that post-translationally modify Tau. Direct interactions with Tau remain to be discovered but some studies suggest that the formation of aggregates may be part of an early neuroprotective process that prevents accumulation of more pathological hyperphosphorylated species. An additional common feature of these studies was the suppression of microglial activation indicating additional anti-inflammatory actions. The beneficial effects of LM11A-31 have been extended to models of Huntington's disease, spinal cord injury, peripheral nerve injury, and others. Overall, the above findings highlight the potential of LM11A-31 for use as an orally bioavailable disease modifying agent in neurodegenerative diseases. The compound is currently under investigation in a phase 2a clinical trial for treatment of AD (ClinicalTrials.gov NCT03069014).

p75^{NTR} ectodomain: In addition to the various functions of the intact p75^{NTR}, its ectodomain is shed from cell surfaces in a physiologically regulated manner. The diffusible p75^{NTR} ectodomain (p75ECD) has neuroprotective actions and has been investigated recently for its potential use in the treatment of AD and frontotemporal dementia. A 2015 study by Yao et al. showed that p75ECD shedding is downregulated in the brains of AD patients and APP/PS1 transgenic AD mice (Yao et al., 2015). Restoration of p75ECD levels in mice expressing the Tau P301L mutation using intracerebroventricular injection of a soluble p75ECD-Fc fusion construct protected against pathological Tau modifications (Shen et al., 2019). Intramuscular delivery of an AAV-p75ECD vector in a mouse APP/PS1 model of AD resulted in better spatial learning and memory, a reduced Aβ burden in the brain and blood and reduced neurite degeneration, neuronal death, microgliosis, inflammation, and Tau phosphorylation (Wang et al., 2016). These important results, taken together, indicate that the p75ECD has neuroprotective properties. In parallel studies, Jiao et al. (2015) investigated the p75ECD as a potential diagnostic marker for AD, finding a distinct p75ECD profile in AD patients compared to patients with stroke, Parkinson's disease, and healthy controls. The profile of decreased CSF levels concomitant with increased serum levels was seen only in the AD group, and these levels were correlated with performance on the mini-mental state examination. These results point to the potential utility of p75ECD levels for early diagnosis of AD and evaluation of disease progression.

Other approaches: Other approaches in various stages of development, summarized in **Additional Table 1**, have pursued therapies based on (1) small molecules that antagonize interactions of p75^{NTR} with itself or effector molecules such as Rho, (2) knockdown of p75^{NTR} by siRNAs and (3) use of neutralizing antibodies. They have shown neuroprotective and anti-inflammatory effects in animal models of TBI (Tat-PEP5, p75 siRNA, EVY 901), subarachnoid hemorrhage (Tat-PEP5), photoreceptor degeneration (neutralizing antibody, THX-B) and peripheral nerve damage (THX-B, PD90780). These studies illustrate the widespread application of p75^{NTR} interventions for many different neurodegenerative conditions. In addition to these specifically targeted therapies, a wide array of studies have explored the regulation of neurotrophin signaling by plant derived bioactive molecules, such as epichatechins, resveritrol and curcuminoids, as well as by existing antipsychotic drugs. These studies have revealed indirect links to the modulation of neurotrophin signaling that continue to be pursued in greater depth as our understanding of p75^{NTR}and neurotrophin signaling advances.

Significance: The above studies highlight the potential value of p75^{NTR} based interventions for neurodegenerative disease modification. Early increases in p75^{NTR} may signal the initial responses of the nervous system to disease-related stress and establish an environment conducive to disease progression by shifting the balance of neurotrophin signaling, not only in neurons but also in immune cells. One of the most important features of p75^{NTR} interventions is the ability to stabilize intracellular calcium, the cytoskeleton, and inflammatory activity which are common early features of many neurodegenerative processes. As such, the interventions have the potential to modify the course of disease prior to development of more severe pathological states. The studies highlighted in this perspective provide groundbreaking work in this area but further studies will be needed to understand the complex and multifaceted actions of the p75^{NTR}. These actions include a potential role in the regulation of Tau and anti-inflammatory activity. Additionally, products of p75^{NTR} activation such as the p75ECD may offer reliable, early biomarkers crucial to the identification of patients who may benefit from early disease modifying therapies. Together, these developments mark the beginning of a new era of neurotrophin-based therapies for the treatment of neurodegenerative diseases.

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Additional files:
Additional Table 1: *Therapeutic approaches for modulation of p75 neurotrophin receptor signaling.*
Additional file 1: *Open peer review report 1.*

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Additional Table 1 Therapeutic approaches for modulation of p75 neurotrophin receptor signaling

Therapeutic entity	Therapeutic strategy and effects
LM11A-31	• Small molecule that binds $p75^{NTR}$ • Bioavailable, with excellent CNS penetration • Neuroprotective and anti-inflammatory effects in animal models of neurodegenerative disease, injury, and infection • Completing phase 2a in participants with mild to moderate Alzheimer's Disease
p75ECD-Fc, AAV-p75ECD	• $p75^{NTR}$ cleavage product, engineered for improved tissue delivery • Neuroprotective and anti-inflammatory effects in animal models of Alzheimer's disease, frontotemporal lobar degeneration, and depression • Effective delivery to the CNS
TAT-Pep5	• Small peptide conjugated to the HIV tat protein for improved tissue penetration • Blocks interaction of $p75^{NTR}$ with cytoskeletal regulatory factor, Rho-GTP • Neuroprotective and anti-inflammatory in animal models of TBI and subarachnoid hemorrhage
p75 siRNA	• Knockdown of $p75^{NTR}$ expression • Neuroprotective in an animal model of TBI
p75 neutralizing antibody	• Antibody to $p75^{NTR}$ • Evidence for neuroprotection after bulbectomy, attenuates photoreceptor degeneration and microglial activation
THX-B	• Small molecule $p75^{NTR}$ antagonist • Protects against diabetic retinopathy, voiding dysfunction, photoreceptor degeneration and retinitis pigmentosa in various animal models
EVY 901	• Small molecule that inhibits $p75^{NTR}$ dimerization • Neuroprotective and anti-inflammatory in an animal model of TBI • Reduces expansion of monocytes in response to LPS
PD90780	• Small molecule that interacts with NGF to prevent binding to $p75^{NTR}$ • Reduces cystitis-induced bladder dysfunction in a rat model

This Additional Table highlights various therapeutic approaches designed to modulate the activity of the p75 neurotrophin receptor. The summary specifically highlights in vivo studies representative of a growing area of research and is not intended to be comprehensive. AAV: Adeno associated virus; CNS: central nervous system; ECD: extracellular domain; Fc: complement binding fragment of IgG; LPS: lipopolysaccharide; siRNA: small inhibitory ribonucleic acid; TBI: traumatic brain injury.