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In vivo functions of p75^{NTR}: challenges and opportunities for an emerging therapeutic target

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Abstract

The p75 neurotrophin receptor (p75^{NTR}) functions at the molecular nexus of cell death, survival, and differentiation. In addition to its contribution to neurodegenerative diseases and nervous system injuries, recent studies have revealed unanticipated roles of p75^{NTR} in liver repair, fibrinolysis, lung fibrosis, muscle regeneration and metabolism. Linking these various p75^{NTR} functions more precisely to specific mechanisms marks p75^{NTR} as an emerging candidate for therapeutic intervention in a wide range of disorders. Indeed, small molecule inhibitors of p75^{NTR} binding to neurotrophins have shown efficacy in models of Alzheimer's disease and neurodegeneration. Here, we outline recent advances in understanding p75^{NTR} pleiotropic functions *in vivo*, and propose an integrated view of p75^{NTR} and its challenges and opportunities as a pharmacological target.

Keywords

Neurotrophin receptors; neurodegenerative diseases; Alzheimer's disease; fibrinolysis; small molecule inhibitors

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Disclosure of potential conflicts of interest

The authors declare no conflicts of interest.

Pleiotropic biological functions of p75^{NTR}

p75^{NTR} plays a central role in a wide range of biological processes including regulation of cell death and survival, scar formation, energy expenditure and the hypoxic response and through these processes contributes to biological functions vital for tissue repair, metabolism and neurodegeneration. These pleiotropic functions have been identified *in vivo* in relevant animal models including neurological, metabolic, and fibrotic diseases. Emerging evidence for the role of p75^{NTR} in Alzheimer's disease (AD), has led to an ongoing clinical trial targeting p75^{NTR} in AD patients. Although these disease-relevant biological functions make p75^{NTR} a promising target for diverse pathologies, they also present challenges due to the pleiotropic functions of p75^{NTR} in the brain and the periphery. The manifold functions of p75^{NTR} *in vitro* have been reviewed extensively elsewhere [1–3]. Here, we provide an overview on the *in vivo* functions of p75^{NTR} and the challenges and opportunities for its pharmacologic targeting in disease.

p75^{NTR} – structure & function

The p75 neurotrophin receptor, or p75^{NTR} (also known as nerve growth factor receptor (NGFR)), was first cloned by Dan Johnson and Monte J. Radeke [4, 5] and recognized as a receptor for all **neurotrophins (NTs)** (see Glossary), including nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and neurotrophin-4 (NT-4). Named according to its molecular mass, p75^{NTR} belongs to the tumor necrosis factor receptor (TNFR) superfamily, and is a single transmembrane-spanning protein with an amino-terminal extracellular domain (ECD) and carboxy-terminal intracellular domain (ICD) with a flexible juxtamembrane adaptor protein-binding region, followed by a globular death domain (DD). Four cysteine-rich domains in the p75ECD control receptor conformation and ligand binding (Figure 1) [6]. The mechanism of p75^{NTR} activation by NTs involves a rearrangement of disulfide-linked receptor dimers, resulting in the separation of intracellular DDs [7]. In addition to all NTs, the p75ECD binds **pro-neurotropins (proNTs)**, amyloid-β (Aβ), prion protein peptide 106–126 (PrP), and rabies virus glycoprotein (RVG) [3, 8]. p75^{NTR} lacks intrinsic catalytic activity, and activates signaling cascades via co-receptors and intracellular adaptor proteins. For example, p75^{NTR} can interact with **tropomyosin-related kinase (Trk)** receptors to enhance its binding specificity and affinity to mature NTs, with NogoR and Lingo-1 to mediate axonal growth inhibitory effects of CNS myelin, with sortilin to initiate apoptosis signaling of proNTs, and with PKA to regulate cAMP [1, 8, 9]. In addition, p75^{NTR} undergoes proteolytic cleavage by α-secretases, such as ADAM metalloprotease and γ-secretase (**regulated intramembrane proteolysis (RIP)**), which releases soluble ICD with cytoplasmic and nuclear signaling functions. The hierarchical activation of p75^{NTR} downstream pathways is determined by competitive protein-protein interactions [10–12]. Indeed, depending on the nature of its co-receptors and cytoplasmic interaction partners, p75^{NTR} mediates diverse and sometimes opposing cellular effects (Table 1, Figure 1, reviewed by [1, 3, 6, 13]).

Cell Death & Survival

The effect of $p75^{NTR}$ on cell death or survival depends upon the ligands and co-receptors [14, 15]. $P75^{NTR}$ null mice have approximately 50% less dorsal root ganglion neurons across different sensory neuron subtypes, which may be due to impaired NT signaling, although the underlying mechanism is unclear [16]. Interestingly, neuron-specific deletion of $p75^{NTR}$ results in no embryonic deficits, but postnatally 20% of neurons are lost selectively within the nonpeptidergic nociceptor lineage, suggesting that $p75^{NTR}$ is required for establishment of postnatal sensory neuron diversity [17]. Inappropriate innervation of sympathetic neuron targets in $p75^{NTR}$ null mice and $BDNF^{+/-}$ mice suggests that BDNF binding to $p75^{NTR}$ might regulate sympathetic pruning. Indeed, *in vivo* experiments in sympathetic eye-projecting neurons revealed that BDNF signaling via $p75^{NTR}$ causes locally-defined axon elimination, largely by inhibiting the TrkA-mediated signaling that is essential for axon maintenance [18]. During development and following injury, $p75^{NTR}$ can act as an apoptotic receptor. ProNT binding to $p75^{NTR}$ can induce apoptosis of oligodendrocytes after spinal cord injury (SCI) [19], of corticospinal neurons after axotomy [20], and of basal forebrain neurons after seizure [21], and blockade of $p75^{NTR}$ reduces ischemic cell death [22]. ProNT activation of $p75^{NTR}$ in Müller glial cells of the retina induces a TNFα-dependent death of retinal ganglion cells in a non-cell-autonomous way [23]. Apoptotic activity of $p75^{NTR}$ induced by proNTs requires interaction with sortilin as a $p75^{NTR}$ co-receptor [24], and signals via activation of caspase-3 [25], in contrast to other death receptors that signal via the extrinsic, caspase-8-dependent pathway. Moreover, NT receptor-interacting factor (NRIF), a $p75^{NTR}$ effector protein, is required for $p75^{NTR}$-mediated apoptosis in sympathetic [26] and hippocampal neurons [27]. Although most studies of $p75^{NTR}$-mediated cell death have focused on proNT-induced cell death, ligand-independent apoptotic signaling by $p75^{NTR}$ has also been shown to promote apoptosis, potentially by dimeric conformational changes [28, 29].

Cell differentiation & Growth

$p75^{NTR}$ is a key player in the regulation of cell differentiation and neuronal growth [3, 30]. $p75^{NTR}$ null embryos show deficits in outgrowth of thoracic intercostal nerves and display delayed development of axonal limb and ophthalmic branches, and $p75^{NTR}$ null adult mice have deficits in sensory and sympathetic target innervation [16, 31]. Unligated $p75^{NTR}$ is a potent activator of RhoA signaling, and NTs suppress this effect. In addition, myelin ligands, such as Myelin Associated Glycoprotein (MAG), can bind to the Nogo receptor (NgR), a GPI-linked $p75^{NTR}$ co-receptor. MAG strengthens the association between $p75^{NTR}$ and the Rho-GDP dissociation inhibitor (Rho-GDI), and prevents Rho-GDI from inhibiting RhoA, thus leading to RhoA activation. Consistent with this model, MAG-induced growth inhibition is attenuated in sensory and cerebellar granule neurons derived from $p75^{NTR}$ null mice. Overall, $p75^{NTR}$ serves as an on/off switch for RhoA activation, and ligands (such as NT and MAG) modulate the level of RhoA activation.

Scar Formation & Regeneration

Scar formation by activated astrocytes and hepatic stellate cells (HSCs) inhibits tissue repair and regeneration in the brain and periphery, respectively [32] (Table 2). $p75^{NTR}$ is expressed in HSCs and astrocytes and is a key regulator of scar formation in liver and brain [33–35]. In the liver, $p75^{NTR}$ regulates regeneration by promoting HSC differentiation into myofibroblasts through activation of the small GTPase Rho [33]. At later stages following injury, secretion of pro-NGF or NGF by regenerating hepatocytes may lead to ligand-induced $p75^{NTR}$-mediated activation of apoptotic pathways in HSCs. These findings have been confirmed in independent rodent models of liver fibrosis [36].

In the brain, expression of $p75^{NTR}$ is upregulated in astrocytes following injury, which promotes reentry into the cell cycle by upregulating CDK2 expression [35], as well as hypertrophic reactivity [34, 35]. Astrocyte $p75^{NTR}$ is cleaved in response to the profibrotic factor transforming growth factor (TGF)-β, and the p75ICD interacts with nuclear pore complex nucleoporins to promote nucleocytoplasmic shuttling of transcription factors required for glial scar formation. Notably, this nuclear pore interaction does not occur in neurons, indicating cell-specific regulation of intramembrane proteolysis of $p75^{NTR}$ might contribute to cell type differences in the composition of the nuclear pore complex and growth factor signal transduction pathways [34].

Fibrinolysis & Tissue Fibrosis

Fibrinolysis is required for fibrin degradation, ECM remodeling and tissue repair, and its inhibition leads to excessive fibrin deposition resulting in inflammation, scar formation, and reduced regeneration [37]. $p75^{NTR}$ inhibits fibrinolysis independent of NTs by interacting with phosphodiesterase PDE4A4/5, which leads to cAMP degradation, reduced PKA activation, downregulation of tissue plasminogen activator (tPA) and upregulation of plasminogen activator inhibitor 1 (PAI-1) [38]. Expression of $p75^{NTR}$ in Schwann cells inhibits fibrinolysis in sciatic nerve injury, whereas $p75^{NTR}$ null mice have increased fibrin clearance and are protected against lung injury [38]. Rolipram, an inhibitor of all PDE4s, reduces fibrin deposition in LPS-induced lung fibrosis [38], and reduces alveolar fibrin deposition in a model of hyperoxia-induced lung injury [39]. In chronic obstructive pulmonary disease (COPD), PDE4A4, the human analog of PDE4A5, is upregulated [40] and is considered a pharmacologic target [41]. Characterization of the $p75^{NTR}$/PDE4A4/5 interaction revealed that it is mediated primarily by a unique region in the extreme C-terminus of PDE4A4/5 not shared by other PDE4 isoforms [9], suggesting PDE4A5-$p75^{NTR}$ interaction is an appealing precision drug target given its well characterized interface and upstream regulators. Further understanding of the cell types and injury states in which $p75^{NTR}$ and PDE4A4/5 are co-expressed might reveal additional opportunities for $p75^{NTR}$-PDE4A4/5 based therapies for fibrin clearance.

Obesity & insulin resistance

$p75^{NTR}$ is expressed in white adipose tissue (WAT), skeletal muscle and liver, and is a central regulator of glucose metabolism and obesity [42, 43]. Genetic loss of $p75^{NTR}$

improves glucose tolerance, increases insulin sensitivity, and significantly improves the suppression of hepatic glucose production by insulin [42]. Furthermore, $p75^{NTR}$ null mice are protected from high fat diet (HFD)-induced obesity and insulin resistance through significantly enhanced energy expenditure, insulin sensitivity in skeletal muscle, hepatic, and adipose tissue [43]. In adipocytes, the p75ICD forms a complex with Rab5 and Rab31 to regulate Glut4 plasma membrane translocation [42]. $p75^{NTR}$ also directly interacts with the catalytic subunit of protein kinase A (PKA) and regulates cAMP signaling in adipocytes, leading to decreased lipolysis and thermogenesis. Adipocyte-specific depletion of $p75^{NTR}$ or transplantation of $p75^{NTR}$-null white adipose tissue into wild-type mice fed a HFD protects against weight gain and insulin resistance, identifying $p75^{NTR}$/PKA signaling as a potential target for therapeutic intervention in insulin resistance and metabolic syndrome [43].

In addition to these peripheral actions, the role of NTs in hypothalamic feeding circuits suggest that $p75^{NTR}$ may also be a candidate to influence food-entrainable behaviors. Indeed, $p75^{NTR}$ expression in neurons within the arcuate hypothalamus is required for food anticipatory behavior in response to daytime-restricted feeding [44]. However, future studies are needed to determine if $p75^{NTR}$ regulates PKA signaling in the CNS, and how $p75^{NTR}$-regulated metabolism and food-entrained clocks impact metabolic health.

Hypoxia

$p75^{NTR}$ undergoes oxygen-dependent cleavage by γ-secretase to provide a positive feedforward mechanism required for the adaptive response to low oxygen tension, a condition known as hypoxia [45]. Cellular adaptation to hypoxia is mediated by the transcription factor hypoxia-inducible factor-1α (HIF-1α), which regulates a battery of genes involved in cell migration, proliferation, angiogenesis, metabolism and inflammation. Stabilization of HIF-1α during hypoxia is controlled by the E3 ubiquitin ligase seven in absentia homolog 2 (Siah-2), which targets prolyl hydroxylases (PHDs) for proteasomal degradation. Reduction in oxygen levels stimulates γ-secretase-dependent release of p75ICD and its interaction with Siah2, which decreases autoubiquitination. Siah2 then targets PHDs for proteasomal degradation, which results in HIF-1α stabilization [45]. Hypoxia and upregulation of Hif1-α contribute to a wide range of diseases including tumorigenesis, ischemic disorders and neurologic diseases, such as Alzheimer's disease (AD) and multiple sclerosis (MS). Regulation of hypoxic responses by $p75^{NTR}$ cleavage demonstrates an oxygen-dependent signaling mechanism upstream of PHDs and ubiquitin ligases. Thus, targeting the hypoxia-dependent cleavage of $p75^{NTR}$ could have wide-ranging therapeutic effects.

$p75^{NTR}$ functions in nervous system pathologies

Central nervous system diseases

Retinal injuries—In the retina, $p75^{NTR}$ has been primarily associated with axon guidance, NT-mediated neuronal apoptosis and ischemic retinopathy. In retina-specific $p75^{NTR}$ null mice, ephrin-A reverse signaling is impaired, disrupting axon repulsion and mapping during visual system development [46]. $p75^{NTR}$ expression is confined to Müller glial cells, where it may reduce Müller cell supportive functions or promote the release of proapoptotic factors

to induce retinal degeneration [23, 47] (Table 2). Supporting this non-cell-autonomous role for $p75^{NTR}$ in retinal degeneration, genetic loss of $p75^{NTR}$ prevents basic fibroblast growth factor (bFGF) reduction and tumor necrosis factor-alpha (TNFα) production by Müller glial cells in response to proNGF, resulting in increased retinal ganglion cell and photoreceptor survival [23].

$p75^{NTR}$ is a major player in ischemic vascular diseases in the eye, such as diabetic retinopathy and oxygen-induced retinopathy, which can cause visual impairment and eventually blindness [48]. $p75^{NTR}$ null mice have decreased stabilization of HIF-1 and VEGF expression, leading to decreased retinal angiogenesis [45]. Thus, in retinal diseases characterized by HIF-1α dysregulation, such as ischemic retinopathy, the p75ICD–Siah2 interaction might be a therapeutic target for regulating oxygen-dependent angiogenesis and tissue remodeling.

Multiple Sclerosis and spinal cord injury

Multiple approaches have been used to investigate the role of $p75^{NTR}$ function in demyelinating diseases, leading to some discrepant results [49, 50]. Although genetic loss of $p75^{NTR}$ does not affect oligodendrocyte death and subsequent remyelination in the MS model of cuprizone-induced demyelination [51], $p75^{NTR}$ can mediate death of oligodendrocyte lineage cells and influence myelinating processes after SCI [19]. These diverging results likely reflect context-dependent differences in $p75^{NTR}$ expression, and the effect of the inflammatory environment. Interestingly, in addition to oligodendrocytes, $p75^{NTR}$ is upregulated in endothelial and perivascular cells of the CNS at the vascular interface in several animal models of MS, suggesting that $p75^{NTR}$ might be crucial for the regulation of blood-brain-barrier integrity and the extent and composition of inflammatory infiltrates during inflammatory demyelination [49, 50, 52]. Although $p75^{NTR}$ impairs neovascularization and blood flow recovery in a mouse model of limb ischemia by suppression of signaling mechanisms implicated in endothelial cell survival and angiogenesis [53], the link between $p75^{NTR}$ expression in injured endothelial and perivascular cells has not been investigated during inflammatory demyelination.

Alzheimer’s disease

A growing body of evidence indicates that $p75^{NTR}$ might contribute to AD pathogenesis [54]. Studies performed on $p75^{NTR}$ deficient mice indicate that Aβ can directly activate $p75^{NTR}$-mediated cell death through the selection of downstream death effectors [55]. AD is also characterized by abnormal aggregation of tau protein, and $p75^{NTR}$ expression has been associated with tau hyperphosphorylation. Antagonizing the binding of Aβ to $p75^{NTR}$ in mouse models of human tauopathies suppresses tau hyperphosphorylation [56, 57]. Moreover, inactive variants of $p75^{NTR}$ internalize more slowly than wild-type $p75^{NTR}$, reducing amyloid precursor protein (APP) internalization and colocalization with beta-site amyloid precursor protein cleaving enzyme-1 (BACE1) and favoring non-amyloidogenic APP cleavage [58]. However, loss of $p75^{NTR}$ has differing outcomes on Aβ-related pathology depending on the AD mouse model [59]. Altogether, these *in vivo* studies favor

a potential mechanism for a feed-forward loop of amyloidogenesis regulated by Aβ/p75^{NTR}/BACE1 interactions in AD.

Interestingly, recent evidence suggests that the soluble p75ECD is protective against Aβ toxicity in AD. p75ECD levels in cerebrospinal fluid and in brains of AD patients and in APP/PS1 (AD) transgenic mice are significantly reduced [60]. The sheddase-TNF-alpha-converting enzyme (TACE, also called ADAM metallopeptidase domain 17 (ADAM17)) is the main enzyme to cleave p75^{NTR} and release its ECD, and TACE activity is significantly reduced in brains of AD mice and CSF of AD patients. Aβ reduces TACE expression and shedding of p75ECD, indicating that reduction of soluble p75ECD in AD is a downstream toxic action of Aβ [60]. Remarkably, restoration of normal p75ECD levels by transgenic expression of human p75ECD before or after Aβ deposition reversed behavioral deficits and AD-type pathologies in a mouse model. Furthermore, transgenic expression of p75ECD also reduced amyloidogenesis by suppressing beta-secretase expression and activity [60]. Overall, these data indicate that p75ECD might act as a neurotoxin scavenger for Aβ and proNTs, preventing their signaling through full-length p75^{NTR} and, therefore, represents a compelling therapeutic target and biomarker in AD.

Cognitive impairment

p75^{NTR} acts as a critical regulator for cholinergic forebrain neuron function and hippocampal synaptic plasticity, which affect learning and memory [15, 61, 62]. Cholinergic neurons highly express p75^{NTR}, and germline deletion of p75^{NTR} increases cholinergic innervation of the hippocampus [63], suggesting that p75^{NTR} is a negative regulator of hippocampal function. However, a more recent study showed that deletion of p75^{NTR} alters cholinergic innervation of barrel cortex but not hippocampus [64]. A key component of working and spatial memory is persistent firing of entorhinal cortex pyramidal neurons. p75^{NTR} controls excitability and persistent firing of the cortical pyramidal neurons in a proNGF-dependent way [65]. p75^{NTR} null mice have improved working memory, but also display increased propensity for severe seizures. Therefore, the proBDNF-p75^{NTR} axis may control pyramidal neuron excitability and persistent activity to balance entorhinal cortex performance with the risk of runaway activity that can result in epileptic seizures [65].

Persistent modifications of synapses include either strengthening or weakening of synaptic connections, respectively termed long-term potentiation (LTP) and long-term depression (LTD). Synaptic plasticity is tightly controlled by NTs, and an emerging concept is that proBDNF and mature BDNF, through their respective p75^{NTR} and TrkB receptor-signaling systems, elicit opposing effects on synaptic plasticity. p75^{NTR} null mice have impairments in several learning and memory tasks [66, 67] and are deficient in LTD [68]. P75^{NTR} null mice also show decreased expression of NR2B, an NMDA glutamate receptor subunit uniquely involved in LTD, and activation of p75^{NTR} by proBDNF enhances NR2B-dependent LTD and NR2B-mediated synaptic currents, suggesting that activation of p75^{NTR} by proBDNF facilitates hippocampal LTD [69, 70]. Interestingly, p75^{NTR} null mice are resistant to age-dependent disruption of hippocampal homeostatic plasticity, as well as age-related memory and cognitive deficits, supporting the notion that p75^{NTR} might mediate age-related increased LTD over LTP [71]. However, cognitive dysfunction of p75^{NTR} null mice could

also be attributed to a role of $p75^{NTR}$ in adult neurogenesis. $p75^{NTR}$ is expressed in subventricular zone and hippocampal progenitor cells, and regulates their cell fate [72]. Newborn neurons generated from hippocampal neural stem cells contribute to hippocampus-dependent learning and memory, and abnormal hippocampal neurogenesis occurs in CNS diseases, such as AD. Collectively, these studies underscore the emerging view of $p75^{NTR}$ as a contributor to cognitive impairment in AD and aging, and highlight $p75^{NTR}$ as an important therapeutic target for limiting AD- and age-related memory and cognitive function deficits.

$p75^{NTR}$ as a pharmacological target

As $p75^{NTR}$ functions through various modes of action, four major classes of $p75^{NTR}$-modulating agents are considered for pharmacologic manipulation: 1) modulators of $p75^{NTR}$ expression, 2) inhibitors of p75ICD interaction with its partners, 3) agents blocking $p75^{NTR}$ cleavage, and 4) agents blocking ligand binding to p75ECD (Figure 2, Table 3).

Genetic tools altering $p75^{NTR}$ expression

In vivo knockdown of $p75^{NTR}$ expression using antisense oligonucleotides prevents sensory neuron degeneration after axotomy in rats when administered to the proximal nerve stump [73], and reduces inflammation and demyelination in an animal model of MS [50]. In the rat retina, shRNA targeting of $p75^{NTR}$ expression prevents proNGF-induced acellular capillary formation [74] and abrogates Müller glia activation and inflammation [75]. Noninvasive intranasal delivery of siRNA blocking the induction of $p75^{NTR}$ expression after traumatic brain injury (TBI) prevents proNT-induced neuronal cell death and preserves sensorimotor function [76], highlighting the potential benefit of inhibiting $p75^{NTR}$ signaling as a therapeutic approach to prevent secondary progressive brain damage after TBI.

Cell-permeable peptides interfering with intracellular signaling

Cell permeable peptides can competitively inhibit interactions of $p75^{NTR}$ with its downstream partners, abrogating $p75^{NTR}$ signaling. **Tat-pep5**, which inhibits the interaction between p75ICD and Rho-GDI and prevents $p75^{NTR}$-induced activation of RhoA, induces axonal regeneration after optic nerve crush [77]. Moreover, Tat-pep5 attenuates isoflurane-mediated loss of synapses in the hippocampus [78], reduces the lesion volume after TBI [79] and improves learning and memory in mice receiving proBDNF infusions in the hippocampus [77, 80].

The soluble form of c29, a 29-amino acid peptide mimic of the cytoplasmic juxtamembrane region of $p75^{NTR}$, inhibits neuronal cell death, whereas the plasma membrane bound c29 peptide induces neuronal cell death, suggesting that membrane localization of the $p75^{NTR}$ cytoplasmic juxtamembrane region is required to activate the death pathway and that c29 can act as a dominant-negative inhibitor of $p75^{NTR}$ death signaling [81]. Acute c29 application to axotomized motor neuron axons decreases cell death, and systemic c29 treatment of $SOD1^{G93A}$ mice, a common model of amyotrophic lateral sclerosis, resulted in spinal motor neuron survival at mid-disease as well as in delayed disease onset [82].

Soluble c29 promoting motor neuron survival is suggested to enhance the activation of TrkB-dependent signaling pathways in neurons in conditions of low-level NT exposure [82].

Blocking p75^{NTR} cleavage

Peptide inhibitors of α-secretase and γ-secretase prevent the proteolytic cleavage of p75^{NTR} and thereby prevent p75ICD-mediated biological functions. Inhibition of p75^{NTR} cleavage by γ-secretase may represent a strategy to counteract p75^{NTR} functions in AD, such as p75ICD-induced cell death. However, γ-secretase processes a wide range of integral membrane proteins, some of them with critical cellular functions, and targeting γ-secretase in AD has failed in clinical trials, resulting in significantly increased risk of serious adverse events [83]. Thus for clinical use, it may be necessary to design secretase inhibitors that selectively lower p75^{NTR} cleavage events without interfering with the cleavage of other important substrates.

Blocking interaction of p75^{NTR} with extracellular ligands

The interaction of p75^{NTR} with NTs can be blocked using small molecules, peptide inhibitors or antibodies [84]. A cyclic decapeptide that mimics the binding site of NGF for p75^{NTR} decreases the size of β amyloid-induced brain inflammation [85], modulates kindling-induced mossy fiber sprouting in a rat model of epilepsy [86] and decreases post-axotomy retinal ganglion cell death [87]. Various antibodies (e.g. REX) can also be used to block NT binding to p75^{NTR}. *In vivo* application of REX results in decreased myelin sheath thickness in sciatic nerve axons by inhibiting BDNF from binding to p75^{NTR} [88], and leads to altered firing patterns and synaptic composition of abducens motoneurons via inhibition of NGF binding to p75^{NTR} [89].

In silico screening has identified small molecule ligands that interact with p75^{NTR} and modulate its signaling pathways, marking a milestone for p75^{NTR} as an emerging candidate for therapeutic intervention [90] (Figure 3). Small molecule ligands (e.g. THX-B, LM11A-24 and LM11A-31) effectively downregulate degenerative and upregulate trophic signaling in animal models of disease, such as in retinal diseases, TBI, SCI, peripheral neuropathy, Diabetes, Huntington's disease, HIV, aging, tauopathy, and AD (Table 3) [47, 91–107]. The small molecule LM11A-31 stimulates the recruitment of interleukin-1 receptor-associated kinase (IRAK) survival adaptor to p75^{NTR} and upregulates downstream NF-κB and Akt pro-survival signaling. LM11A-31 significantly improves bladder function and promotes functional recovery after SCI [91, 108], reverses spatial memory impairments after TBI [92], ameliorates cisplatin-induced peripheral neuropathy [93], prevents diabetes-induced retinal vascular permeability [94], and suppresses neurodegeneration in HIV and aging [95]. LM11A-31 also interferes with proNT degenerative signaling, promoting survival signaling through p75^{NTR} to inhibit/reverse AD degeneration and slowing progression of AD [96–100], and LM11A-31 inhibits multiple aspects of the development of tau pathology, including degeneration of neurites and spines [100, 101]. The effectiveness of altering p75^{NTR}-coupled signaling networks and in reversing neurite/spine degeneration with a lack of apparent deleterious effects in preclinical studies indicate that LM11A-31 modulation of p75^{NTR} may be an approach with significant therapeutic potential.

Excitingly, a modified formulation of LM11A-31 is currently being tested in a phase IIa exploratory endpoint trial in subjects with mild to moderate AD (Clinical Trial Number[i]: NCT03069014).

Additional agents have expanded the umbrella of potential pharmacological approaches targeting $p75^{NTR}$ in nervous and non-nervous system disorders. These include the lateral olfactory tract usher substance (LOTUS), which promotes axonal regeneration after optic nerve crush injury and inhibits NgR1-mediated signaling by interfering with the interaction between NgR1 and $p75^{NTR}$ [109], EVT901, a novel piperazine derivative inhibiting $p75^{NTR}$ oligodimerization, which is neuroprotective, modulates central and peripheral inflammation and improves functional outcome in a model of TBI [110, 111], lithium citrate, which is a potential inhibitor of proNGF and protects hippocampal neuronal cell death [112], and the small molecule NSC49652, which inhibits tumor growth in a melanoma mouse model by targeting the transmembrane domain of $p75^{NTR}$, inducing receptor activation and cell death in melanoma cells [113].

Concluding Remarks

Given the fundamentally improved understanding of its *in vivo* functions and induced expression in a wide range of neurological and peripheral diseases, $p75^{NTR}$ represents an emerging target for drug discovery. Small molecule compounds that modulate $p75^{NTR}$ ligand binding are of great interest, and have already shown efficacy in CNS injuries and disease, in particular in mouse models of neurodegenerative diseases (Figure 2). Since $p75^{NTR}$ has pleiotropic functions, it will be important to identify if $p75^{NTR}$-driven diseases share common $p75^{NTR}$ mechanisms to optimize pharmacological approaches targeting of the molecule (see Outstanding Questions). Notably, some $p75^{NTR}$ functions are ligand-independent, indicating that blocking ligand binding may only partially inhibit $p75^{NTR}$ signaling and could potentially leave some detrimental functions of $p75^{NTR}$ intact. Therefore, it will be important to differentiate ligand-dependent cell surface $p75^{NTR}$ signaling from signaling by cleaved fragments, and to define the molecular pathways and interaction sites of intracellular mediators of $p75^{NTR}$ in disease. Targeting specific intracellular mediators of $p75^{NTR}$, which are required for both ligand-dependent and independent signaling, may have better therapeutic potential than blocking only ligand-dependent signaling. By defining the intracellular mediators of $p75^{NTR}$ signaling and the mechanisms by which they interact with $p75^{NTR}$, it may be possible to selectively block its deleterious functions while retaining its beneficial effects. Patients with devastating conditions stand to benefit from the successful development of these agents.

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[i]Resources
https://clinicaltrials.gov/ct2/show/NCT03069014

Glossary

Neurotrophins (NTs)
NTs are a family of proteins that regulate survival, development and function of neurons. The term NT is more generally reserved for four structurally related factors: Nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and neurotrophin-4 (NT-4).

Pro-neurotrophins (proNTs)
Neurotrophins are synthesized as precursor proteins that are proteolytically cleaved to form mature neurotrophins. ProNT cleavage can occur either intracellularly by the action of furin or proconvertase, or extracellularly by the action of plasmin, matrix metalloproteinase MMP-7 or MMP-9.

Regulated intramembrane proteolysis (RIP)
$p75^{NTR}$ is subject to proteolytic cleavage, first by a peptidase- mediated ectodomain shedding, leaving a membrane bound C- terminal fragment (p75CTF) and liberating the ECD, and then by the γ-secretase complex that targets the p75CTF, releasing a soluble intracellular domain (p75ICD) with signaling capabilities.

TAT-Pep5
A 15-amino acid residue peptide (Pep5; CFFRGGFFNHNPRYC) with the binding site mapped onto a hydrophobic patch framed by helices 5 and 6. Pep5 fused with the amino (N)-terminal protein transduction domain (11 amino acids) from the human immunodeficiency virus protein TAT (TAT–Pep5) competitively inhibits the interaction between p75ICD and Rho-GDI.

Tropomyosin-related kinase (Trk)
Family of tyrosine kinases that regulates survival, differentiation, synaptic strength and plasticity in the mammalian nervous system. NTs are common ligands of Trk receptors. Each type of NT has different binding affinity toward its corresponding Trk receptor.

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Outstanding Questions

- Which diseases require $p75^{NTR}$ and would benefit from pharmacologic targeting of $p75^{NTR}$?
- Which are the integrative $p75^{NTR}$ functions shared by major neurodegenerative diseases?
- What are the relative contributions of ligand-dependent $p75^{NTR}$ signaling versus intracellular signaling by cleaved $p75^{NTR}$ fragments in CNS diseases?
- Which molecular pathways and interaction sites of intracellular mediators of $p75^{NTR}$ signaling can be harnessed for the development of drugs to promote the $p75^{NTR}$ beneficial effects?
- Can we design drugs to achieve selective targeting of $p75^{NTR}$ signaling profiles for specific disease applications?

Highlights

- $p75^{NTR}$ is a driver of disease pathogenesis in neurological, metabolic, and fibrotic diseases.
- $p75^{NTR}$ is highly pleiotropic interacting with multiple ligands, co-receptors, and signaling molecules.
- Blockade of $p75^{NTR}$ binding to its ligands or intracellular partners has therapeutic potential.
- Tissue-specific selective targeting of $p75^{NTR}$ may avoid potentially adverse on-target effects.

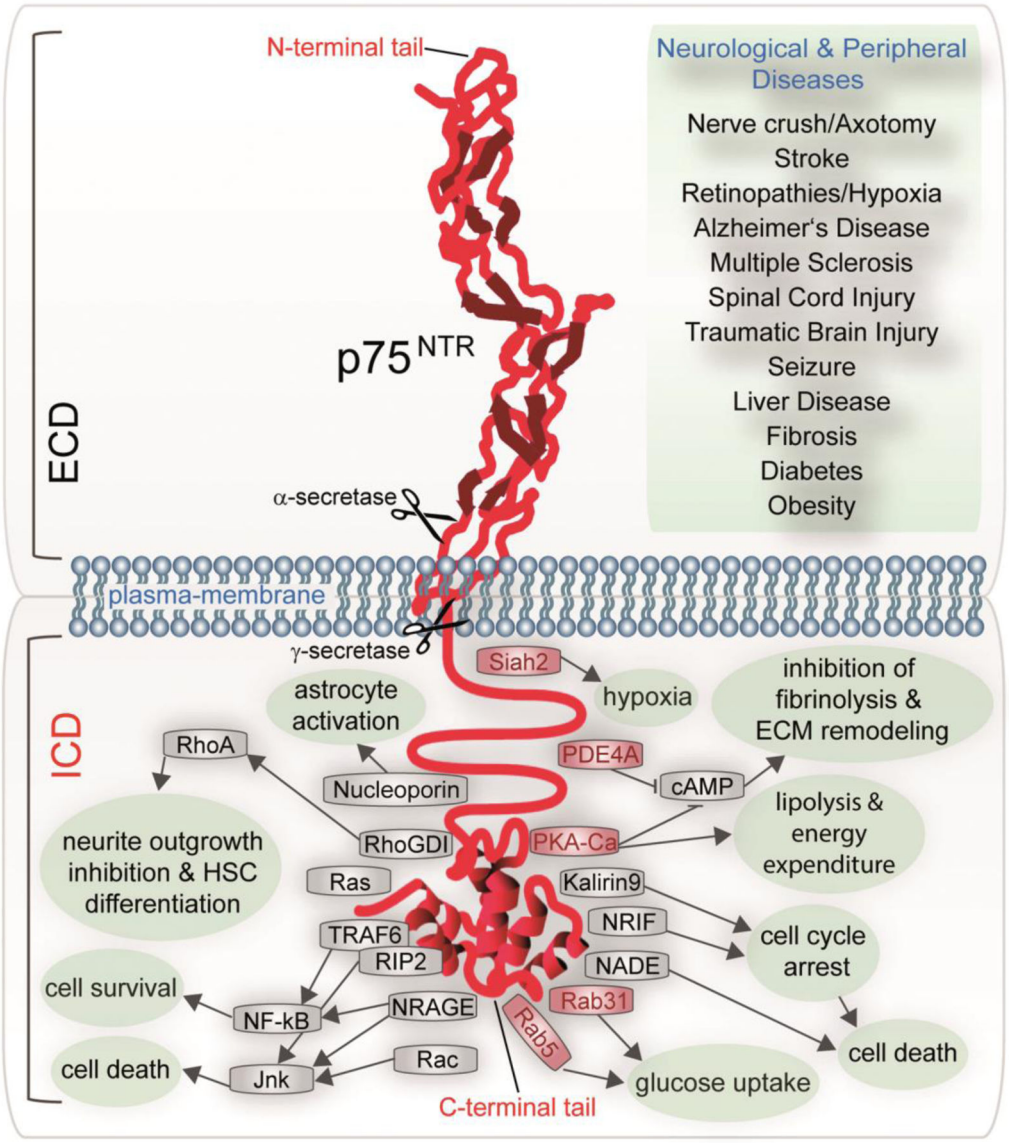

Figure 1. p75^{NTR} structure and adaptor proteins involved in signaling.

p75^{NTR} is a single transmembrane-spanning protein with an amino-terminal ECD and a carboxy-terminal ICD. The ECD consist of 4 CRDs involved in ligand binding. The TM is involved in membrane sorting of p75^{NTR}. The ICD consists of the juxtamembrane adaptor protein-binding region, the DD and the C-terminal tail. p75^{NTR} is subject to proteolytic cleavage releasing a soluble ICD with signaling capabilities. Selected p75^{NTR} catalytic (red, serine-threonine kinases, protein tyrosine phosphatase, ligase and small GTPase), and non-catalytic (grey, scaffolding- and adaptor-like molecules) partners mediate diverse cellular effects, such as neurite outgrowth inhibition & HSC differentiation, cell survival, cell death, glucose uptake, cell cycle arrest, inhibition of fibrinolysis, hypoxia, lipolysis, energy expenditure, and ECM remodeling (see list of p75^{NTR} interactors in Table 1, reviewed by [1, 3, 6, 13]). **Abbreviations:** p75^{NTR}; p75 neurotrophin receptor, ECD; extracellular domain,

TM; transmembrane domain, ICD; intracellular domain, DD; death domain, CRD; cysteine rich domain. HSC; hepatic stellate cell, ECM; extracellular matrix.

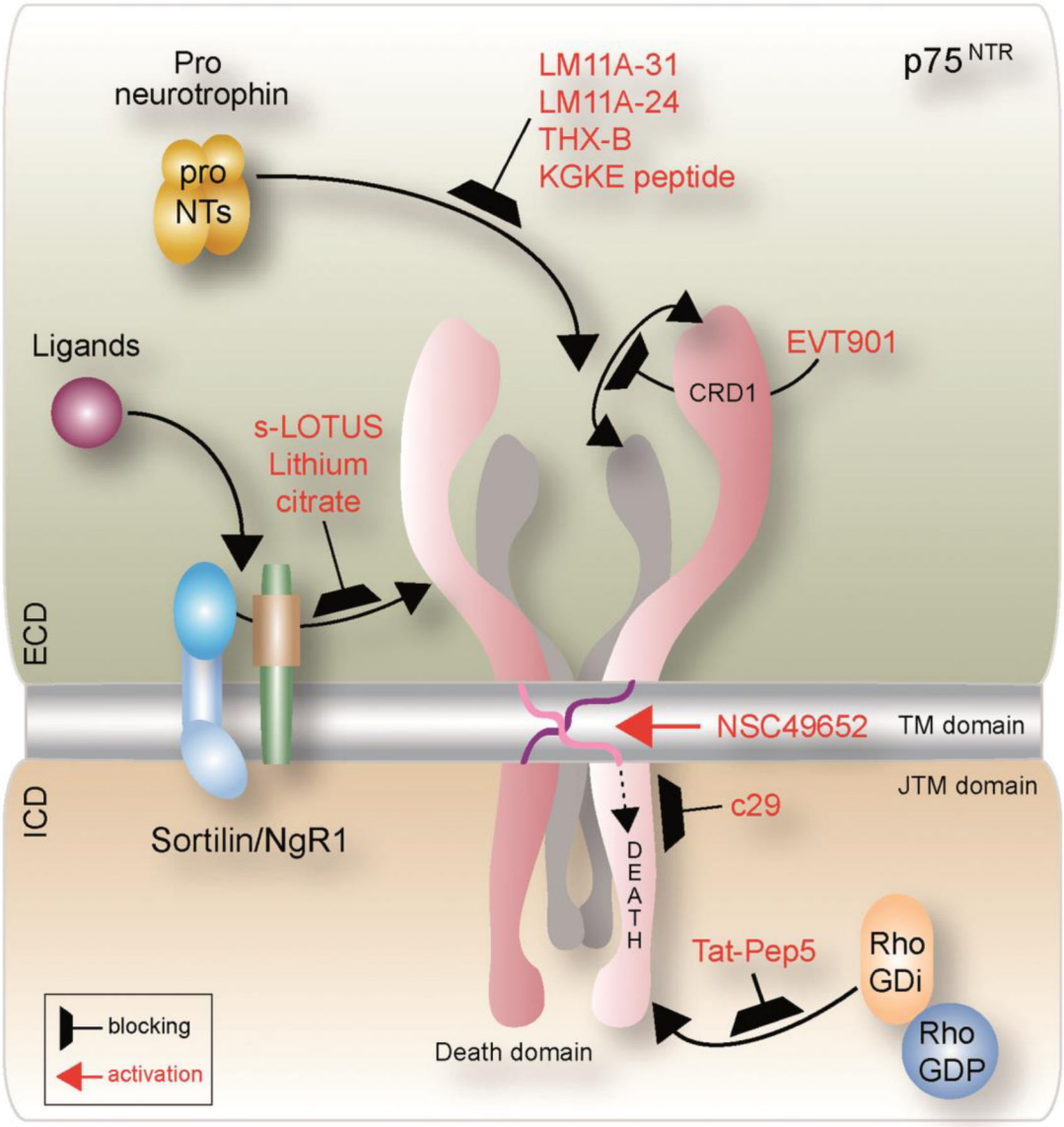

Figure 2. Mechanism of action of p75^{NTR} - modulating small molecule compounds.

LM11A-31, LM11A-24, THX-B and the KGKE peptide or homologous sequence inhibit proNT binding to p75^{NTR}, EVT901 interacts with the p75^{NTR} CRD1 and inhibits p75^{NTR} pre-oligomerization, NSC49652 interacts with the p75^{NTR} TM domain and induces conformational changes and p75^{NTR} activity, lithium citrate prevents the association of the p75^{NTR}-sortilin receptor complex, s-LOTUS inhibits the interaction between NgR1 and p75^{NTR}, the c29 peptide inhibits p75^{NTR} cytoplasmic juxtamembrane death signaling, and the TAT-Pep5 peptide inhibits p75ICD and Rho-GDI interaction (see list of p75^{NTR} modulating small molecule compounds and peptides in Table 3). **Abbreviations:** p75^{NTR}; p75 neurotrophin receptor, ECD; extracellular domain, TM domain; transmembrane domain, ICD; intracellular domain, JTM domain; juxtamembrane domain, CRD1; cysteine rich domain 1, NgR1; Nogo receptor 1.

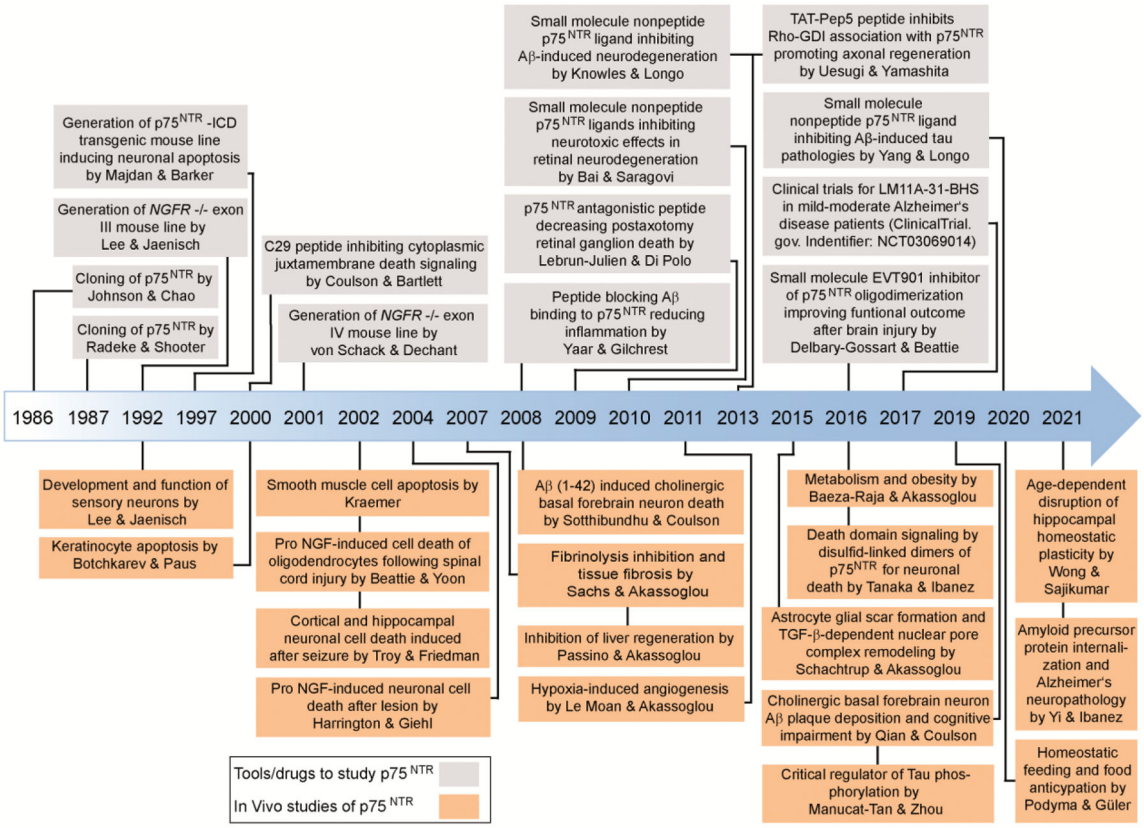

Figure 3. Milestones of *in vivo* functions and drug targeting of p75^{NTR}.

Timeline of the discovery, *in vivo* studies in preclinical models of neurological and peripheral diseases, and the development of tools/drugs to study p75^{NTR}. Milestones in this timeline are cited in references [4, 5, 11, 16, 19, 25, 33–35, 38, 42, 43, 47, 57, 58, 71, 100, 110, 128, 140–148].

Table 1

$p75^{NTR}$ interacts with several partners including small GTPases, ubiquitin ligases and FG-Nups.

Protein	$p75^{NTR}$ domain	Function	Refs
Caveolin-1	unknown	Neuronal differentiation	[114]
TRAF2, 4	TRAF2 DD TRAF4JX	Cell death	[115]
TRAF6	JX	Schwann cell apoptosis	[116]
NRIF1/2	JX and DD	Cell death	[117]
FAP-1	DD	Schwann cell apoptosis	[118]
SC1	JX	Neuronal cell growth	[119]
NRAGE	JX	Neuronal cell death	[120]
Bex3/NADE	DD	Cell death	[121]
RIP2	DD	Schwann cell apoptosis	[122]
ARMS	ICD (domain unknown)	Neuronal cell death	[123]
Necdin	DD	Neuronal cell death	[124]
PLAIDD	DD (2nd helix)	Cell death	[125]
IRAK	unknown	Cell death	[126]
Rac	unknown	Oligodendrocyte apoptosis	[127]
Rho-GDl	DD (5th helix)	Neurite outgrowth	[128]
RanBPM	DD	unknown	[129]
C-Cbl	unknown	unknown	[130]
Ras GTPase	DD (5th helix)	Neurite outgrowth	[131]
Bex1	unknown	Neuronal differentiation	[132]
PDE4A5	JX	Matrix remodeling	[38]
Kalirin9	DD (5th helix)	Neurite outgrowth	[133]
SaII2	DD	Neurite outgrowth	[134]
SIAH2	JX	Hypoxic response	[45]
APR-1	JX	Melanoma cell apoptosis	[135]
Rab5	DD (4th helix)	Adipocyte glucose uptake	[42]
Nup153	DD	Astrocyte nucleo-cytoplasmic shuttling	[34]
PKA subunits RIIβ and Cα	DD (5th & 6th helix)	Adipocyte lipolysis, energy expenditure	[43]
NIX	JX	Neuronal cell death	[136]

Abbreviations: DD: death domain, JX: juxtamembrane domain

Table 2

p75^{NTR} *in vivo* functions in development and disease.

		Disease	Cellular Expression	Functions	p75 ^{NTR} −/− phenotype	Refs
Nervous system	Injuries	Spinal cord injury	Oligodendrocytes Neurons	Cell death/survival	Increased oligodendrocyte survival & reduced neuronal survival	[19, 137]
		Traumatic brain injury		Cell death/survival	Reduced lesion volume & improved motor coordination	[79]
		Nerve crush/ axotomy	Schwann cells Oligodendrocytes	Cell death/survival Cellular differentiation	Reduced axonal growth & myelination	[88, 138]
		Retinopathies	Müller cells RGC	Cell death/survival Angiogenesis	Protection from retinal ganglion cell death Reduced neoangiogenesis	[23, 45]
		Stroke/Ischemic disorders	Astrocytes Neurons	Cell death/survival Cell cycle regulation	Reduced infarct volume	[22, 139]
	Neurodegenerative disorders	Alzheimer's disease	Cholinergic neurons	Cell death/survival	Improved cognition Protection from amyloidogenesis Reduced cell death	[55, 59, 140]
		Multiple Sclerosis	Astrocytes Endothelial cells Perivascular cells Oligodendrocytes	Cell death/survival EC proliferation / Adhesion	Increased inflammation No change in cell death	[49, 51]
		Seizure	Neurons	Cell death/survival	Reduced cell death	[21]
Non nervous system		Liver disease	Hepatic Stellate Cells	Myofibroblast differentiation	Impaired liver regeneration	[33]
		Lung fibrosis	Smooth Muscle Cells	Fibrinolysis	Protection from fibrin deposition & lung fibrosis	[38]
		Diabetes	Adipocytes	Glucose uptake	Increased glucose uptake & insulin sensitivity	[42]
		Obesity	Adipocytes	Energy balance and lipolysis	Protection from weight gain & metabolic syndrome	[43]

Table 3

$p75^{NTR}$ modulating small compounds and peptides.

Pharmaceutical tools	Animal model	Target cell type	Functions	Phenotype	Refs
LM11A-31	Alzheimer's disease	Neurons	Neuroprotective Synaptic resilience	Reduced Aβ-associated degeneration of neurites and spines	[100]
		Microglia	Inflammation	Reduced microglia activation	[99]
		Neurons	Neuroprotective	Reduced tau pathology, neuroinflammation and neurodegeneration	[98]
		Cholinergic Neurons	Neuroprotective	Prevented basal forebrain cholinergic neuron neurodegeneration	[97]
		Neurons	Neuroprotective	Reduced cognitive deficits and neurodegeneration	[96]
	Aging	Neurons	Neuroprotective	Reduced basal forebrain cholinergic neuron degeneration	[102]
	Huntington's Disease	Neurons	Neuroprotective	Reduced brain atrophy, plasma cytokine level, and urinary $p75^{NTR}$ ECD level	[103]
		Neurons	Neuroprotective	Reduced Htt aggregation, spine loss and improved cognition, motor performance and survival	[104]
	Tauopathy	Neurons	Neuroprotective Synaptic resilience	Reduced synaptic degeneration and improved hippocampal behavior outcome	[100, 101]
	Traumatic brain injury	Neurons Neural stem cells	Cell survival Neurogenesis	Reduced neuronal death, impairment of neurogenesis, and spatial learning deficits	[92]
	Spinal cord injury	Oligodendr ocytes Neurons	Cell survival	Reduced oligodendrocyte cell death and myelinated axons	[91]
	Seizure	Neurons	Cell survival	No effect on hippocampal cell death	[105]
	Cisplatin-induced peripheral neuropathy	Neurons	Neuroprotective	Prevented decreases in peripheral nerve function	[93]
	Diabetes	Endothelial cells	Retinal barrier protective	Preserved blood-retina barrier integrity	[94]
	HIV	Neurons Microglia	Neuroprotective	Reduced neurodegeneration	[95]
LM11A-24	Alzheimer's disease	Neurons	Neuroprotective	Reduced tau pathology, neuroinflammation and neurodegeneration	[98]
	Optic nerve axotomy Glaucoma	Retinal ganglion cells	Cell survival	Preventing loss of retinal structure	[47]
THX-B	Retinitis pigmentosa	Photorecep tor cells	Neuroprotective	Reduced photoreceptor cell loss	[106]
	Diabetic retinopathy	Müller glial cells	Neuroprotective	Reduced Müller glia activation, retinal ganglion cell loss and maintained blood-retina barrier integrity	[107]
	Optic nerve axotomy Glaucoma	Retinal ganglion cells	Cell survival	Preventing loss of retinal structure	[47]

Pharmaceutical tools	Animal model	Target cell type	Functions	Phenotype	Refs
EVT901	Traumatic brain injury	Neuron Oligodendr oocytes Myeloid cells	Neuroprotective Inflammation	Increased neuronal and oligodendrocyte survival and reduced inflammation	[110, 111]
Lithium citrate	Seizure	Neurons	Cell survival	Increased hippocampal neuronal survival	[112]
NSC49652	Melanoma	Melanoma cells	Cell death	Increased cell death of melanoma cells	[113]
s-LOTUS	Optic nerve crush	Retinal ganglion cells	Neuronal regeneration	Promoting axonal regeneration	[109]
KGKE peptide or homologous sequence	Neuroinflam mation	Microglia, Astrocytes	Activation	Reduced β amyloid-induced brain inflammation	[85]
	Optic nerve axotomy	Retinal ganglion cells	Cell survival	Promoting retinal ganglion cell protection	[87]
	Epilepsy	Mossy fiber pathway	Synaptic reorganization	Blocking mossy fiber sprouting in the inner molecular layer	[86]
TAT-Pep5 peptide	Optic nerve crush	Retinal ganglion cells	Neuronal regeneration	Promoting axonal regeneration	[77]
	Isoflurane-induced neurodegen eration	Neurons	Neuroprotective	Reduced loss of hippocampal synapses	[78]
	Aging	Neurons	Neuroprotective	Improved learning and memory	[80]
c29 peptide	Developmen tal cell death	Retinal ganglion cells	Neuroprotective	Reduced retinal ganglion cell death	[81]
	Amyotrophic lateral sclerosis	Motor neurons	Neuroprotective	Inhibition of motor neuron death	[82]