P75NEURO

First-in-class Effective and Safe Fusion Protein Drugs for Patients with Neurological Diseases

Overview

Drug Name	P75NEURO
Description	Chronic neurodegenerative diseases such as Alzheimer's and Parkinson's diseases, as well as the acute conditions such as stroke and neurotrauma, degenerate the functions of the neuronal systems continuously as the diseases progress. The resulting social and economic burdens are enormous. To tackle the unmet needs, P75NEURO, a fusion protein drug that consists of the extracellular domain of p75 (p75ECD) and an immunoglobulin fragment C, was developed. P75NEURO prevents p75 neurothrophin receptor (p75NTR) from binding to various neurotrophic factors or nerve growth factors to antagonize the neurotoxic effects of p75NTR. Both *in vitro* and *in vivo* tests showed that P75NEURO was safe and efficacious with good druggability profile including good DMPK profile, stability in plasma (9 days of half-life), and no adverse effects at the effective dose.
Target	p75NTR (also named nerve growth factor receptor, NGFR)
Drug Modality	Fusion protein
Indication	Ischemic stroke; Alzheimer's disease; Traumatic brain injury; Inflammatory pain
Product Category	Neurotrophic agent; Signal transduction modulator
Mechanism of Action	P75NEURO antagonizes the neurotoxic effects of the p75NTR.
Status	Preclinical
Patent	Patents on using P75NEURO for the treatment and diagnosis of neurological diseases have been filed.

Seeking Global Collaboration

Protheragen Inc. is actively seeking partnership and licensing deals to further develop P75NEURO.
We look forward to collaborating with you soon.

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Target

p75NTR (NGFR)

Introduction	The extracellular domain of the nerve growth factor receptor (NGFR) includes four 40-amino acid repeats with 6 cysteine residues at conserved positions followed by a serine/threonine-rich region, a single transmembrane domain, and a 155-amino acid cytoplasmic domain. The cysteine-rich region contains the nerve growth factor binding domain.
Approved Name	Nerve growth factor receptor
Official Symbol	NGFR
Gene Type	Protein coding
Synonyms	CD271; p75NTR; TNFRSF16; p75(NTR); Gp80-LNGFR
Ensembl	ENSG00000064300
Gene ID	4804
mRNA Refseq	NM_002507
Protein Refseq	NP_002498.1
OMIM	162010
UniProt ID	P08138
Chromosome Location	17q21.33

Clinical Resources

Gene Function	p75NTR has 3 transcripts (splice variants), 245 orthologues, and 21 paralogues.
Pathway	p75NTR is a low affinity receptor that can bind to neuron growth factor (NGF), brain derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and neurotrophin-4 (NT-4). It mediates the neuronal cell survival and death.
Major Conditions	Neurological disorders; Cancer

Indication

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Neurological Diseases

Neurological diseases, also known as neurological disorders or nervous system diseases, refer to a small class medical conditions affecting the nervous system. Stroke, Alzheimer's disease, and traumatic brain injury all belong to this category. As a neuroprotective agent, P75NEURO can hinder or prevent the development of nervous system diseases by protecting the neurons from injuries. In addition, P75NEURO has potential therapeutic values for the cardiovascular disease and inflammatory pain.

Ischemic stroke	Stroke is a leading cause of morbidity and mortality on a global scale, a trend that is expected to continue as a result of the economic transition in the low- and middle-income countries. Referring to central nervous system infarction accompanied by overt symptoms, ischemic stroke accounts for almost 85% of all stroke events. According to the American Heart Association/American Stroke Association, total annual stroke-related costs are expected to reach USD 240.67 billion by 2030, a 129% increase over the cost at 2012. Acute intervention for ischemic stroke involves the administration of thrombolytic agents to restore perfusion and/or neuroprotective agents to limit neuronal damage.
Alzheimer’s disease	Alzheimer's disease (AD) is a slowly progressive and ultimately fatal degenerative brain disorder that primarily affects the elderly. AD is the most common cause of dementia and accounts for 60% to 80% of the cases. According to Lancet Commission’s estimate, approximately 47 million people worldwide were living with dementia, including AD, in 2017 and predicted that this number would triple by 2050. The financial costs attributable to AD and other forms of dementia are USD 818 billion globally in 2015. At 2018, the global social costs of dementia toped USD 1 trillion. While available therapies are often effective in palliating symptoms and improving quality of life, existing drugs do not target the underlying disease pathology and are not capable of prolonging survival.
Traumatic brain injury	Traumatic brain injury (TBI) results from a sudden and violent impact to the head or when an object penetrates the skull and enters the brain tissue. It frequently occurs as a consequence of motor vehicle accidents, falls, sports injuries, or violent assaults. However, TBI is a complex and continuous disease process characterized by both structural damage and functional consequences. An international team has calculated a higher estimate of 69 million (range 64 to 74 million) episodes of TBI

worldwide each year. TBI costs the global economy approximately USD 400 billion annually, equivalent to approximately 0.5% of the entire annual gross world product.

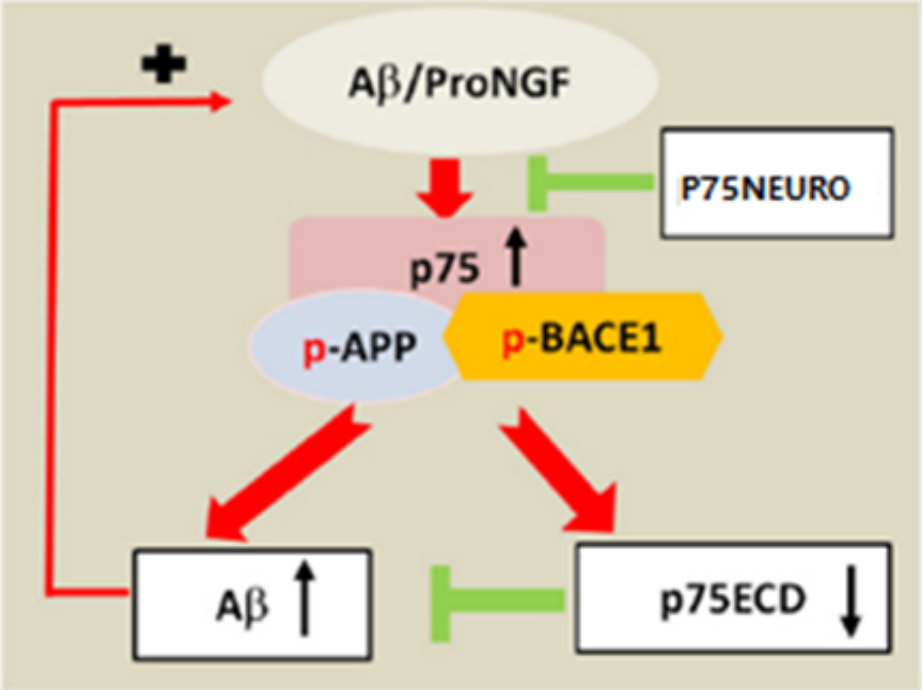
A person suffering traumatic brain injury should receive immediate medical attention. Stabilization and treatment may prevent secondary injury.

Mechanism of Action

P75NEURO antagonizes the neurotoxic effects of the p75NTR

P75 neurotrophin receptor (p75NTR), a receptor for brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and nerve growth factor precursor protein (proNGF), regulates the neuronal growth and death. P75NTR is also a receptor for β-amyloid (Aβ). The extracellular domain of p75 (P75ECD) is an endogenous neuroprotective protein that actively blocks the progression of neurodegeneration in neurological diseases. A dimer fusion protein consisted of P75ECD and Fc fragment of human immunoglobulin, P75NEURO inhibits the secretion of inflammatory cytokines and prevents the binding of p75NTR to Aβ and proNGF by:

- Blocking amyloidogenesis by preventing β-amyloid precursor enzyme-1 (BACE1) expression and endocytosis;
- Blocking tau hyperphosphorylation induced by both Aβ and proneurotrophins.



Status

The Patent Status of p75NEURO

Patents on using P75NEURO for the treatment and diagnosis of neurological diseases have been filed in Australia and through patent cooperation treaty (PCT).

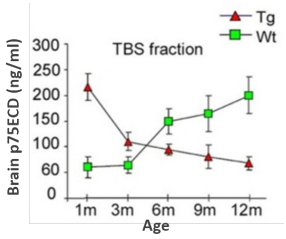
	Discovery/Optimization	Pre-clinical	Phase I	PhaseII	PhaseIII	NDA Filed
p75NEURO						

Data

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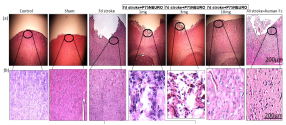
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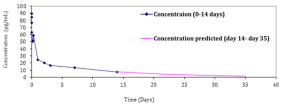
p75NTR as A Therapeutic Target

Transgenic mouse models of Alzheimer's disease (AD) accurately mimic human neurotrophic imbalance and AD pathology: brain levels of p75ECD were found to increase with age in wild-type and reduce in transgenic AD mice.



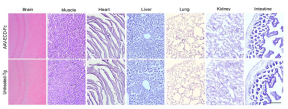
Treatment of P75NEURO in Ischemic Stroke

P75NEURO showed dose-dependent neuroprotection in rat ischemic stroke models. Sensory and motor functions in stroke rats have been improved significantly by P75NEURO. Its neuroprotective role was also confirmed in hypoxia-ischemic treatment. Furthermore, P75NEURO was demonstrated to promote neurite outgrowth and suppress neuronal apoptosis after oxygen glucose deprivation (OGD).



Pharmacokinetics Study of P75NEURO

The concentration profile after a single intravascular administration of 3mg/kg of P75NEURO in stroke rats is shown in the figure. The half-life of P75NEURO *in vivo* is around 9 days.
In addition, P75NEURO has demonstrated the characteristics of high stability, solubility, and bioavailability.



Toxicity Study of P75NEURO

No systemic or organ-specific adverse effects were observed in mice following the P75NEURO treatment.

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