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<p>(54) Title: PHARMACEUTICAL FORMULATIONS OF CNTF</p> <p>(57) Abstract</p> <p>Pharmaceutical formulations of ciliary neurotrophic factor (CNTF) are described which are useful for therapeutic treatment of damage to the peripheral nervous system. Formulations of CNTF ideally suited for intrathecal administration are provided.</p>		

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PHARMACEUTICAL FORMULATIONS OF CNTF

TECHNICAL FIELD OF THE INVENTION

5 This invention relates to pharmaceutical formulations of ciliary neurotrophic factor suitable for therapeutic treatment of damage to the peripheral nervous system.

10 BACKGROUND OF THE INVENTION

 The peripheral nervous system consists of those nerve cells that extend axonal processes outside the spinal cord and brain. The principle nerve cell types in the peripheral nervous system are primary motor
15 neurons innervating skeletal muscle and controlling movement, autonomic neurons (both sympathetic and parasympathetic) innervating the cardiovascular system and other internal organs and regulating their function, and sensory neurons innervating sensory
20 receptors throughout the body and conveying sensations including pain and proprioception.

 Conditions that compromise the survival and proper function of one or more of these types of peripheral nerve cells cause peripheral nerve damage. Such nerve
25 damage may occur from a wide variety of different causes. Nerve damage may occur through physical injury, which causes the degeneration of the axonal processes and/or nerve cell bodies near the site of injury. Nerve damage may also occur because of
30 temporary or permanent cessation of blood flow to parts of the nervous system, as in stroke. Nerve damage may also occur because of intentional or accidental exposure to neurotoxins, such as the cancer and AIDS
35 chemotherapeutic agents cisplatin and dideoxycytidine (ddC), respectively. Nerve damage may also occur because of chronic metabolic diseases, such as diabetes or renal dysfunction. Nerve damage may also occur because of neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, and

Amyotrophic Lateral Sclerosis (ALS), which result from the degeneration of specific neuronal populations.

Neurotrophic factors are naturally occurring proteins that promote the survival and functional activities of nerve cells. Neurotrophic factors have been found in the target cells to which an innervating nerve cell connects. Such target-derived neurotrophic factors regulate the number of contacts formed between innervating nerve cells and the target cell population, and are necessary for the survival and maintenance of these nerve cells.

Neurotrophic factors are also found in cells that are not innervated. An example of such a neurotrophic factor is CNTF. Human CNTF and the gene encoding human CNTF are described in detail in U. S. patent numbers 4,997,929, and 5,141,856, which are specifically incorporated herein by this reference.

Although the biological role of CNTF has not been conclusively established, CNTF appears to be released upon injury to the nervous system and may limit the extent of injury or neuronal damage. Highly-purified CNTF has been shown to support the survival in cell cultures of chick embryonic parasymphetic, sympathetic, sensory, and motor neurons. There is significant evidence to support that CNTF is a neurotrophic factor for peripheral primary neurons in vivo and in vitro. U. S. patent application serial number 07/735,538 filed July 23, 1991, specifically incorporated herein by reference, shows the surprising effectiveness of systemically administered CNTF to accelerate local recovery at the site of peripheral nerve damage.

The ability of CNTF to protect motor neurons from lesion-induced death may also make it effective in preventing nerve cell degeneration associated with such neurodegenerative diseases as Parkinson's disease, Alzheimer's disease, Amyotrophic Lateral Sclerosis

(ALS), and Spinal Muscular Atrophy (SMA). U.S. patent application serial number 08/015,218 filed February 8, 1993 and U.S. patent application serial number 08/116,440 filed September 3, 1993, both of which are
5 entitled Methods for Treating Amyotrophic Lateral Sclerosis With CNTF, are specifically incorporated herein by reference. These patents present evidence demonstrating the effectiveness of treating amyotrophic lateral sclerosis in humans with CNTF. In addition,
10 Sendtner *et al.* (1990) *Nature* 345:440-441, showed that local application of CNTF prevents lesion-induced death of motor neurons in the rat facial brain stem nucleus. Oppenheim *et al.* (1991) *Science* 251:1616-1618, showed that CNTF promoted the *in vivo* survival of chick spinal
15 motor neurons.

A major problem with the delivery of a therapeutically effective amount of CNTF to a patient for treatment or prevention of peripheral nerve damage is the instability of CNTF in solution. CNTF in
20 solution rapidly precipitates when agitated or subjected to thermal incubation. To the extent that any of the protein is denatured, the effective amount of biologically active CNTF is diminished. Protein integrity must therefore be maintained during
25 manufacture and storage as well as during administration. Proteins are particularly prone to degradation at elevated temperatures. Excipients known to physically stabilize proteins in solutions appear to negatively affect the thermal stability of CNTF.

30 In addition, CNTF is subject to loss from solution by nonspecific adsorption to the surface areas of storage containers and dispensing devices. Such nonspecific binding may occur to a variety of materials including glass and plastics, for example, polyethylene
35 or polypropylene. These materials may be in the form of vials, tubing, syringes, implantable infusion devices, or any other surface which may come in contact

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