



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>C07K 14/475, A61K 38/18</b>	<b>A1</b>	(11) International Publication Number: <b>WO 95/22560</b>  (43) International Publication Date: 24 August 1995 (24.08.95)
<p>(21) International Application Number: PCT/US95/02153</p> <p>(22) International Filing Date: 21 February 1995 (21.02.95)</p> <p>(30) Priority Data: 08/200,243 22 February 1994 (22.02.94) US</p> <p>(71) Applicant: THE SYNTEX-SYNERGEN NEUROSCIENCE JOINT VENTURE [US/US]; 1885 33rd Street, Boulder, CO 80301-2546 (US).</p> <p>(72) Inventors: DIX, Daniel, B.; 1183 Twin Peaks Circle, Longmont, CO 80503 (US). KOSKY, Andrew, A.; 2958 Alice, Newbury Park, CA 91320 (US). FREUND, Erwin; 801 South County Road 21, Berthoud, CO 80513 (US).</p> <p>(74) Agents: SWANSON, Barry, J. et al.; Swanson &amp; Bratschun, L.L.C., Suite 200, 8400 East Prentice Avenue, Englewood, CO 80111 (US).</p>	<p>(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).</p> <p><b>Published</b> <i>With international search report.</i></p>	
<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>		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

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 parasympathetic, 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 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, 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 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 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 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.

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 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

# Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

## Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

## Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

## Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

## API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

## LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

## FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

## E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.