A Novel ER Beta Ligand Prodrug to Treat MS and Other Neurodegenerative Diseases

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OTHER INFORMATION

KEYWORDS

Multiple sclerosis, estrogen receptor beta, ER, ERß, neuroprotection, central nervous system, CNS, blood-brain barrier, small molecule therapy

CATEGORIZED AS

- **Medical**
  - Disease: Autoimmune and Inflammation
  - Disease: Central Nervous System
  - New Chemical Entities, Drug Leads
  - Therapeutics

RELATED CASES

2017-168-0

SUMMARY

Researchers from the Department of Neurology and the Department of Chemistry and Biochemistry at UCLA have developed a novel ERβ ligand prodrug that is structurally designed to more easily cross the blood-brain barrier for treatment of multiple sclerosis.

BACKGROUND

Multiple sclerosis (MS) is an autoimmune disease characterized by inflammation and demyelination of the central nervous system. Current MS treatments have immunomodulatory effects and reduce relapse rates in MS patients, but have only modest effects on disability progression. Recent studies have shown that treatment with estrogens or estrogen receptor (ER) specific-ligands in the mouse model for MS (experimental autoimmune encephalomyelitis (EAE)) are neuroprotective and could ameliorate the effects of MS. Specifically, ERβ ligand-treated animals exhibited preserved axons and myelin compared with vehicle-treated animals. Unfortunately, the concentration of diarylpropionitrile (DPN), the generic ERβ ligand, needed to ameliorate EAE in mice is relatively high. The required dosage results in high off-target effects and is therefore unsafe for clinical use. The need for such large amounts of this drug to treat MS is speculated to be a result of low passage through the blood-brain barrier. In order for ERβ ligands to become clinically useful in the treatment of MS, they must have increased blood-brain barrier permeability and be effective at lower concentrations.

INNOVATION

Researchers at UCLA from the Department of Neurology and the Department of Chemistry and Biochemistry have developed a novel ERβ ligand prodrug that crosses the blood-brain barrier more effectively than DPN. Dosing with this ERβ ligand prodrug results in lower peripheral blood concentration of ER✔ ligand, thereby lessening the exposure of breast, uterus and other off-target tissues to the active molecule. After the drug moves into the central nervous system, it is cleaved and becomes active, resulting in higher brain and spinal cord concentrations over the hours that follow.

APPLICATIONS

- Monotherapy for multiple sclerosis

ADVANTAGES

- Neuroprotective
- Greater impact on permanent disabilities such as cognitive dysfunction, walking problems, balance problems, visual loss, or other symptoms than currently available drugs
- Increased ability to cross blood-brain barrier compared to other ERβ ligands
- Effective at lower concentrations

STATE OF DEVELOPMENT

In vivo testing on mouse model of MS (EAE) shows that initial concentrations of active drug were lower in the blood but increased in the central nervous system over multiple hours. The novel ERβ ligand prodrug was also more effective at treating EAE in mice.

PATENT STATUS

Country	Type	Number	Dated	Case
United States Of America	Issued Patent	11,622,954	04/11/2023	2017-168
Switzerland	Issued Patent	3509583	06/30/2021	2017-168
Germany	Issued Patent	60 2017 041 407.7	06/30/2021	2017-168
France	Issued Patent	3509583	06/30/2021	2017-168
United Kingdom	Issued Patent	3509583	06/30/2021	2017-168
United States Of America	Issued Patent	10,980,767	04/20/2021	2017-168

Additional Patent Pending

RELATED MATERIALS

▶ Wisdom AJ, Cao Y, Itoh N, Spence RD, Voskuhl RR. Estrogen receptor-ß ligand treatment after disease onset is neuroprotective in the multiple sclerosis model. J Neurosci Res. 2013;91(7):901-8.

ADDITIONAL TECHNOLOGIES BY THESE INVENTORS

▶ Pregnancy Hormone-Containing Combination Products for the Continuous Treatment of Autoimmune Diseases

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