USPTO coversheet:
Collaborative deferred-fee provisional patent application pilot program for COVID-19 invention, 85 Fed. Reg. 58038 (September 17, 2020)

Identification number	DFPUB_63198249
Date of filing	10/06/2020
Date available to public	10/28/2020
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Title of invention	Non-invasive vagus nerve stimulation during sleep to aid in COVID-19 recovery: a novel electroceutical approach
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Non-invasive Vagus Nerve Stimulation During Sleep to Aid in COVID-19 Recovery: A Novel Electroceutical Approach

ABSTRACT

The field of neuroimmunology has become an exciting arena for electroceutical innovation. Over the past two decades, there has been expansive development in our understanding of neuroanatomical, cellular, and molecular mechanisms that mediate central modulation of immune functions through the autonomic nervous system. The discovery that vagus nerve stimulation (VNS) caused a prominent attenuation of the systemic inflammatory response evoked by endotoxin in experimental animals was a driving force for growth in this field [3]. Considering the pro-inflammatory response coinciding with COVID-19 infection, VNS has become a prime therapeutic strategy.

Non-invasive transcutaneous vagus nerve stimulation (tVNS) methods that have advanced the treatment of disorders such as epilepsy, depression, and chronic tinnitus [6] are gaining traction as potential electroceutical alternatives for COVID-19 patients [2]. This methodology, though promising, focuses on the immunological effects elicited via tVNS during awake administration. There is unexplored potential in tVNS to facilitate and restore immune homeostasis during sleep by optimizing the processes responsible for filtering metabolites that occur as a result of the neuroinflammatory response [9].

FIELD OF THE INVENTION

As an emerging treatment for COVID-19, the field of non-invasive VNS therapeutics currently focuses on its propensity to mitigate hyper-immune responses. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the inception of the worldwide COVID-19 pandemic, is linked to a corresponding cytokine storm in some critical patients with COVID-19. This storm is characterized by the release of high levels of pro-inflammatory cytokines such as interleukin (IL)-1 β, IL-6, tumor necrosis factor (TNF), and chemokines by respiratory epithelial and dendritic cells, and macrophages [1]. Through the actions of the choroid plexus (CP), these inflammation biomarkers are removed from the central nervous system into cerebral spinal fluid (CSF) during normal sleep cycles. Enhancing this filtration process is a viable, though thus far ignored, therapeutic target for tVNS.

Present studies focus on the modulatory effectiveness of tVNS, specifically its ability to dampen cytokine storm via activation of the vagal-driven cholinergic anti-inflammatory pathway (CAP). As a neuromodulatory therapy it is U.S. Food and Drug Administration approved for acute and preventive treatment of migraine and cluster headaches. It is CE marked in the EU for the treatment and prevention of symptoms of numerous respiratory conditions including: asthma, bronchoconstriction, exercise-induced bronchospasm, and chronic obstructive pulmonary disease (COPD)[2]. Alleviating symptoms of respiratory distress and reducing inflammation constitute the current field of COVID-19 tVNS research.

BACKGROUND OF INVENTION

The choroid plexus (CP) is an epithelio-endothelial complex comprising a highly vascularized stroma with fenestrated capillaries and a continuous lining of epithelial cells joined by apical tight junctions that are crucial in forming the blood-cerebrospinal fluid (B-CSF) barrier. Integrity of the CP is critical for maintaining brain homeostasis and B-CSF barrier permeability [4]. Through its regulation and production of cerebrospinal fluid the CP facilitates the removal of metabolic by-products and the exchange of biomolecules into and out of the brain. Recent experimental and clinical research has revealed the significance of the CP in the pathophysiology of various diseases affecting the CNS. The CP is involved in the penetration of various pathogens into the CNS, as well as the development of neurodegenerative (e.g., Alzheimer´s disease) and autoimmune diseases (e.g., multiple sclerosis) [4,9].

As previously stated, the foundation of current tVNS research regarding COVID-19 is the targeted activation of the cholinergic anti-inflammatory pathway. Stimulation of the vagus nerve has far-reaching implications for cholinergic signaling in other cellular populations within the brain and is not limited to its CAP initiation, however. Cholinergic signaling mechanisms are involved in mediating the function of the choroid plexus, which has been found to express markers of multiple nicotinic acetylcholine receptor (nAChR) subtypes in a region-specific fashion [5].

Optimizing CP function in this manner is viable in part because other cranial nerve stimulation treatments have proven effective and well-tolerated by patients during sleep.

Hypoglossal nerve stimulation (HNS) involves an implantable pacemaker-sized pulse generator that senses chest wall movement during sleep and contracts the genioglossus muscle via stimulation of the hypoglossal nerve. HNS recipients report decreased sleepiness and obstructive sleep apnea effects, and improved quality of life [7,8].

SUMMARY OF THE INVENTION

Recent studies have proposed the key to reducing patient suffering and overall improved health outcomes is utilizing tVNS to ameliorate the over-activity of the immune reaction in response to COVID-19 infection. However, these studies are limited to the awake cycle stimulation protocols utilized in other pathology cases. Administering tVNS while the patient sleeps offers a novel and exciting frontier for electroceutical advancement and possible adjunctive therapy that can be prescribed for numerous neuroimmunological ailments and disorders.

This methodology has additional therapeutic implications:

- restoring brain homeostasis following stroke and trauma
- regulating transferrin secretion in the brain
- facilitating stem cell production and adult neurogenesis
- attenuating symptoms of hydrocephalus
- eliminating CSF biomarkers for Alzheimer's disease
- reducing metabolites linked to neuroinflammatory disease/conditions

DESCRIPTION OF THE PREFERRED EMBODIMENT

Currently, tVNS can be applied either superficially to the cervical nerve using a specially designed device or to specific sites on the ear. Rationale for tVNS applied to the ear (transcutaneous auricular VNS, taVNS) is based on anatomical studies demonstrating that certain parts of the ear area (concha and lower half of the back ear over the mastoid process) have afferent VN distribution [6].

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Doc Code: CV19.PUB.PRO
Document Description: COVID-19 Collab Database Request for Prov Appl

PTO/SB/452 (09-20)

CERTIFICATION AND REQUEST FOR COVID-19 PROVISIONAL PATENT APPLICATION PROGRAM

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First Named Inventor:	Dewey C. Brown II
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APPLICANT HEREBY MAKES THE FOLLOWING CERTIFICATIONS AND REQUESTS THAT THE USPTO INCLUDE THE DESCRIPTION OF THE ACCOMPANYING PROVISIONAL PATENT APPLICATION IN A PUBLIC DATABASE.

1. The description of the accompanying provisional patent application concerns a product or process relating to COVID-19 and such product or process is subject to an applicable FDA approval for COVID-19 use.

2. The accompanying application is in the English language.

3. The accompanying application is being filed in DOCX format via the USPTO's Patent Center filing system, together with this form.

4. The applicant understands that while the required filing fee for the accompanying provisional application may be deferred by acceptance into this program, the appropriate filing fee must be paid in order for a subsequent U.S. nonprovisional application to claim the benefit of the filing date of the accompanying provisional application. Applicant recognizes that the filing fee due in the future may be more than the current fee due and that by deferring payment of the filing fee, there may be an increase in the total fee due.

5. Applicant authorizes and requests that the description, including the specification and any drawings, claims and/or abstract of the accompanying provisional patent application, as well as this form, be included in a searchable online public database.

6. Applicant understands that inclusion in the public database is a publication of the description and this form.

Signature Dewey Brown	Date 10/06/2020
Name (Print/Typed) Dewey C. Brown II	Practitioner Registration Number

Note: *This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required.**

■ *Total of 2 forms are submitted.

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