Succinate Receptor 1 (SUCNR1) Antagonists to Treat Neuroinflammation

A promising therapeutic target for the prevention and/or treatment of neurodegenerative diseases.

Technology Overview

The inventors have identified a small molecule Succinate Receptor 1 (SUCNR1) antagonist (termed “compound 7a”) that interferes with SUCNR1 signaling in microglia and suppresses neuroinflammation. In recent work, the inventors have developed an oral topical gel-formulation of compound 7a, which has been shown to reduce both periodontitis and central nervous system (CNS) inflammation and may represent an efficacious therapeutic agent for the prevention and/or treatment of neurodegenerative diseases. As described in unpublished proof-of-concept (POC) studies, oral treatment with compound 7a reduces neuroinflammation in a mouse model of periodontitis by decreasing levels of the cytokine IL1β both systemically and locally in gingiva, hippocampus, and cerebellum.

Current Development Stage

Lead-like compounds are currently being tested in mouse-model POC studies.

Background

Both chronic neuroinflammation and immune dysregulation in the periphery represent key contributors to the development and progression of non-hereditary neurodegenerative diseases, such as Alzheimer’s disease, Parkinson’s Disease, and Multiple Sclerosis. These diseases can be induced and/or accelerated through dysbiosis (homeostatic imbalance) of microbiota in the mouth and gut, leading to abnormal activation of host immune responses and dissemination of pro-inflammatory cytokines and other signaling compounds into the CNS. Among these, succinate, a common metabolite of mammalian and bacterial cells, has been found to exert a pro-inflammatory response in the CNS through the activation of Succinate Receptor 1 (SUCNR1) and its downstream signaling pathway. Therefore, inhibition of SUCNR1 represents a promising therapeutic strategy to block succinate-mediated, pro-inflammatory signaling cascades and prevent and/or treat neurodegenerative diseases. Such treatments could be further augmented with microbiome-targeted therapeutics to restore succinate homeostasis.

Applications

Category

Life Sciences/Biochemicals & Small Molecules
Life Sciences/Neuroscience
Life Sciences/Therapeutics/Inflammat
Disease
Doug Brawley

Authors

Xin Li, PhD
Deepak Saxena, MS, PhD

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- **Neurodegenerative conditions:** Alzheimer's disease, Parkinson's disease, Multiple Sclerosis, and Amyotrophic Lateral Sclerosis, among others
- **Periodontitis**
- **Potential therapeutic target for oxidative and metabolic stress-related conditions:** Atherosclerosis, metabolic syndrome, and diabetes complications (e.g., osteoporosis, retinopathy, and hypertension)
- **Potential therapeutic target for chronic inflammatory conditions:** Ulcerative colitis and rheumatoid arthritis

Advantages

- **Target topology is favorable for pharmacological intervention:** SUCNR1 is a membrane G protein-coupled receptor with an extracellular surface accessible to drug targeting
- **Method of compound administration:** Compound 7a can be administered orally
- **Well-characterized, disease-implicated signaling pathway:** The succinate/SUCNR1 signaling pathway has been previously implicated in multiple conditions, including ulcerative colitis, rheumatoid arthritis, diabetic retinopathy, hypertension, liver fibrosis and atherosclerosis
- **New therapeutic target for neuroinflammation:** There are no FDA-approved drugs targeting SUCNR1 or the succinate/SUCNR1signaling pathway

Intellectual Property

A U.S. non-provisional application and a PCT application have been filed covering the chemical composition of the compounds and their method of use.