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ENTERIN

Enterin: treating Parkinson's disease by restoring gut–brain neural communication

ENT-01, an orally administered compound in phase 2 trials, is being developed to repair the dysfunctional gut–brain axis in patients with neurodegenerative disease.

The concept of the gut–brain axis is well-established in Parkinson's disease (PD), with decades of research drawing a clear link between the organs. Now, Enterin, Inc. is preparing to leverage that link to treat neurodegenerative disorders through the restoration of neural communication between the gut and the brain.

Enterin's efforts center on the enteric nervous system (ENS), perhaps the major sensory organ of the brain. While the brain pulls in information from the eyes, ears and other sense organs, it receives a much larger volume of signals from the gastrointestinal tract via the ENS. These signals help the brain to manage a range of processes, including sleep–wake cycles, hunger and satiety, bowel motility and autonomic functions such as blood pressure and body temperature.

In PD, neural messaging from the gut to the brain is muffled. Researchers identified a link between the gut, ENS and PD decades ago, leading to recent breakthrough studies that singled out α-synuclein (α-S) as the agent behind this connection.

Enterin's research has shown that α-S is a defensive protein induced in the ENS in response to viral gastrointestinal infections in childhood. Research suggests the protein facilitates immune responses against viral infections but when produced in excess over time its propensity to aggregate creates problems.

Accumulation and aggregation of excessive amounts of α-S cause the ENS to become dysfunctional. At first, the problems this creates are local to the gut, as shown by the presence of constipation in people decades before being diagnosed with PD. But over time, α-S spreads from the enteric nerves via the vagus nerve and the sympathetic chain to the brain.

As α-S spreads, it damages nerve cells, starting in parts of the brain that manage sleep and the autonomic nervous system before affecting the centers that oversee mobility. The accumulation of α-S in the circuits linking the gastrointestinal tract to the brain thereby stops the flow of information required for the normal functioning of the body.

Targeting the gut to treat Parkinson's disease

This understanding of the pathology of PD suggests that targeting neurotoxic aggregates of α-S in the gastrointestinal tract may restore enteric nerve cell function and neural communication with the brain. Such actions may potentially slow the progression of the neurological symptoms of PD and restore gastrointestinal function.

Michael Zasloff and Denise Barbut founded Enterin, based in Philadelphia, Pennsylvania, to explore that opportunity. Since then, Zasloff, the chairman and CEO, and Barbut, the president and CMO, have worked with the third cofounder, senior VP of research and development Bill Kinney, to establish Enterin at the forefront of efforts to repair the dysfunctional gut–brain axis in patients with neurodegenerative disease.

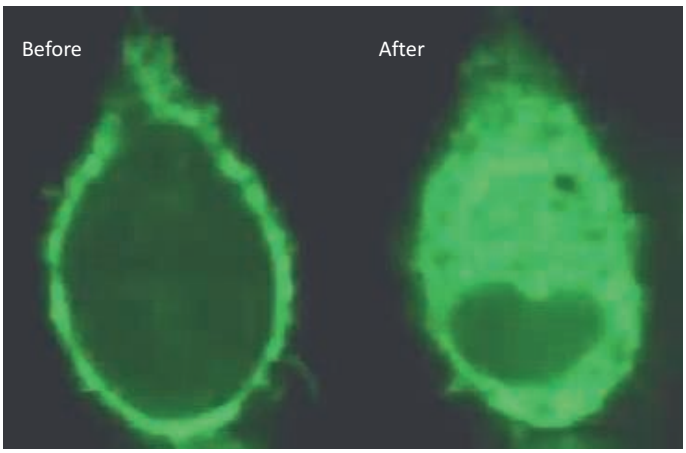

Fig. 1| Action of ENT-01 inside the cell. A protein similar in biophysical characteristics to α-synuclein is expressed in this macrophage-like cell and adheres electrostatically to the negatively charged cytoplasmic surface of the plasma membrane (before). Within seconds of the addition of ENT-01 to the medium, ENT-01 enters the cell, binds to the cytoplasmic face of the membrane and displaces the protein into the cytoplasm (after).

The gut–brain axis is often discussed in the context of the microbiome but Enterin is taking a different approach. Notably, Enterin aims to treat PD with a compound that acts locally in the gut, rather than relying on the bloodstream to send molecules to the brain.

Enterin is developing an orally administered compound that targets the enteric neuron, displacing α-S from intracellular membrane-binding sites, restoring nerve excitability and preventing α-S aggregation. Preclinical studies in mouse models of PD have demonstrated that ENT-01 stimulates colonic motility in a dose-dependent fashion by increasing the excitability of specific neurons within the ENS. Increased excitability of these neurons results in an increase in electrical signaling between the ENS and the brain (**Fig. 1**).

These data supported the advance of ENT-01 into a phase 2a study that assessed the effect of the drug on the bowel function and neurological symptoms of 50 patients with PD and constipation. Oral administration of ENT-01 safely and rapidly restored bowel function in most patients. The trial also linked ENT-01 to improvements in neuropsychiatric symptoms, including hallucinations and delusions, suggesting that directly targeting enteric α-S pharmacologically might be beneficial in PD beyond gut-associated symptoms. These data have been submitted for publication.

In January 2019, Enterin began a larger, double-blind, placebo-controlled study in patients with PD and constipation. The phase 2b study will provide a more complete look at the effect of ENT-01 on bowel function and neurological symptoms.

Moving into phase 3

Enterin expects to complete the phase 2b study in June 2019 and initiate phase 3 trials early next year. To fund the phase 3 studies and its pipeline of preclinical ENS candidates, Enterin plans to raise a mezzanine round in June of this year.

This sequence of events makes the coming year a big period for Enterin and the broader concept of treating PD via the gut. If successful, Enterin stands to address a major unmet need using a safe, novel approach that could benefit a range of neurological conditions.

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