ENDECE Neural LLC

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ENDECE neural
neurological drug development

Modulation of cellular homeostasis as a potent discovery platform

By developing a drug library based on nuclear receptor ligands, ENDECE Neural yielded a lead compound shown to repair and reverse demyelination of nerves in a preclinical model. The compound has the potential to revolutionize the treatment of multiple sclerosis.

Within living cells, as in any efficient system, there are numerous biological pathways that when altered cure disease and therefore present multiple opportunities to restore balance and health. ENDECE Neural has a drug discovery library designed to tap that inherent homeostatic quality to counteract disease mechanisms. The company's approach has led to the discovery of NDC-1308, a promising, new and potentially complementary treatment for multiple sclerosis (MS). "We look at drug development differently," said ENDECE Neural CEO James Yarger. "There are multiple genes and multiple pathways, and we went in search of finding a way to rebalance a disease condition."

Multiple Sclerosis

While the company has amassed a library of candidates, ENDECE is focusing on NDC-1308 as its lead compound based on its demonstrated potential to repair and reverse damage caused by the demyelination of nerves, a severe pathology associated with MS and other neurological diseases. ENDECE recently received a $225,000 Fast Forward grant from the National Multiple Sclerosis Society to advance the clinical development of NDC-1308, an estradiol analog. In addition, the company recently described the remyelinating potential of NDC-1308 in an oral presentation at the 29th Congress of the European Committee for Treatment and Research in Multiple Sclerosis in Copenhagen.

NDC-1308 is a small molecular chemical entity that, unlike other estrogens, is capable of inducing oligodendrocyte progenitor cells (OPCs) to mature into cells that form the myelin sheath around nerve axons. Loss of the myelin sheath leads to some of the most severe symptoms of MS such as sensory impairments (including unclear vision), coordination difficulties, gait problems and difficulties with bodily functions (for example, insufficient bladder control). By focusing on remyelination, ENDECE's approach to treating MS drastically differs from those of marketed therapies that address the autoimmune and inflammatory aspects of MS pathology. NDC-1308 could potentially be used in combination with anti-inflammatory therapies already on the market. Another favorable characteristic of NDC-1308 is its ability to cross the blood-brain barrier. "This allows our drug to reach the tissues in the brain and spinal cord, where promoting myelin production is needed," said Steven Nye, vice president of discovery at ENDECE.

ENDECE is leveraging decades of accumulated knowledge about how activation of estrogen receptors in different manners affects gene regulation. "If you Google 'estrogen receptor and disease', a large number of diseases come up," Nye noted. That is because activation of an estrogen receptor allows it to translocate into the nucleus, bind to DNA and activate sets of genes in various signaling pathways. ENDECE researchers have therefore focused on designing ligand structures that affect the activation of the nuclear receptors to regulate the activity of different genes, including those related to the cell signaling pathways for OPC differentiation. The company has generated and is characterizing the biological function of over 40 estrogen receptor-related compounds. Notably, although evidence suggests that estriol and estradiol may be capable of initiating OPC differentiation, neither can complete the process. Only NDC-1308 both initiates and completes the process of OPC differentiation into mature oligodendrocytes that are capable of making the myelin sheath.

In analyzing results from microarray studies using three different human cell lines, ENDECE found that subsets of its estradiol analogs distinctly affect the transcription of genes in signaling pathways that control cell fate, including OPC differentiation. "When a particular subset of our compounds was analyzed, the upregulation of key genes related to oligodendrocyte progenitor cells and myelin sheath synthesis leapt out at us," said Yarger, who, along with his wife Jean, cofounded ENDECE Neural to focus on taking NDC-1308 through proof-of-concept in preparation for filing an investigational new drug (IND) application.

A Path to an IND

ENDECE Neural's business model is to develop therapeutic compounds through proof-of-concept and phase 1 studies and then to form partnerships for completing clinical studies. The company's working model for NDC-1308 is that the compound induces remyelination by activating estrogen receptors in a specific manner to upregulate genes that are vital to promoting the differentiation of OPCs into mature oligodendrocytes that synthesize and maintain the myelin sheath. This mechanism of action was endorsed when NDC-1308 induced isolated OPCs to differentiate into mature oligodendrocytes in culture, whereas estriol and estradiol, the structurally similar comparators, did not ($P < 0.01$). NDC-1308 also demonstrated a dramatic upregulation of genes (5- to 75-fold) in signaling pathways related to OPC differentiation and myelin sheath production.

Following on from cell culture and *in vitro* studies, NDC-1308 produced some remarkable results in animal models. "To achieve proof of concept, we needed to show it works in the remyelination study," Yarger said. ENDECE enlisted the expertise of Bruce Trapp, chair of the neurosciences department at the Cleveland Clinic, to perform proof-of-concept studies in a cuprizone mouse model of demyelination. The model manifests toxic demyelination when mice are fed a diet containing the copper chelator cuprizone, ingestion of which leads to oligodendrocyte death and loss of the myelin sheath from axons. After demyelination, a 2-week course of NDC-1308 (50 mg/Kg once daily) was associated with a 20% increase in remyelination of hippocampal regions of the brain in mice that were fed the cuprizone diet ($P < 0.01$). "NDC-1308 has a very robust therapeutic effect of promoting remyelination," said Trapp, who has been working with the cuprizone model for many years. Consistent with the gene expression data and the mouse cuprizone data, NDC-1308 increased remyelination in demyelinated rat brain slices in cultures, which were stained to highlight myelin basic protein.

ENDECE Neural is currently advancing the preclinical development of NDC-1308 with a validation study to confirm that the compound can restore and repair the myelin sheath. The validation study will repeat previous testing in mice using an optimized formulation to determine how robustly NDC-1308 can stimulate remyelination in different regions of the mouse brain. Results from pharmacokinetic and safety validation studies will form the basis for an IND application. Ultimately, if NDC-1308 is shown to induce remyelination in clinical studies, it may be possible to improve the lives of patients with MS. If NDC-1308 is successfully developed and marketed, its availability may potentially double the size of the current market for MS therapeutics.

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