FIGHT MND.

Project

Developing a monoclonal antibody modulating CD38 against MND

This project will perform preclinical safety tests needed to advance a drug called NC-B8 toward a clinical trial for MND patients. Investigators have demonstrated that targeting a molecule located on motor neurons and their supporting cells with NC-B8 may benefit MND in three ways: 1) removing harmful built-up protein clumps in motor neurons; 2) restoring motor neuron activity; and 3) reducing the immune response linked to MND.

A positive outcome for this study will be to obtain all data needed to transition NC-B8 to a phase 1 clinical trial for people living with MND in 2023.

About ENCEFA

ENCEFA is a biotechnology company with laboratories located in Maisons-Alfort (2 miles south of Paris), in the neuromuscular diseases building at the National French Veterinary school.

It was co-founded in 2016 by Dr Laurence Bressac (CEO), Dr Serge Guerreiro (CTO) and Dr Toulorge (CSO) with the ambition of developing therapies to fight neurodegenerative diseases, including MND. The foundation of the lab was to transform in vitro discoveries (made with Dr Serge Guerreiro while Dr Toulorge was completing his PhD) into a product that could provide benefit to patients and improve their quality of life.

The first years at ENCEFA have been dedicated to obtaining a better understanding of the mechanism of action in vitro and in vivo, and then to identify a product able to trigger the identified mechanism of action. This led to the discovery of NC-B8, the lead, humanized anti-CD38 monoclonal antibody, which is now 18 months away from clinical development.

Project Lead

Dr Damien Toulorge

ENCEFA, France

When Dr Damien Toulorge and his team identified a new neuroprotective mechanism of action that demonstrated efficacy in experimental models of MND, Parkinson's disease, and Multiple sclerosis, they were at first *"disease agnostic"*.

However, when they observed that in addition to protecting neurons, their compound was also able to protect muscle cells and repress inflammation (thus act simultaneously on all the organs impacted by MND), they realised they had discovered something unique. The decision was made to focus their research primarily on MND, where their drug, NC-B8, has the potential to be game-changing.

NC-B8 compared to other MND drugs

Dr Toulorge says that in conducting their research, at first they obtained proof-of-concept of efficacy in neurons that were not motor neurons.

"Our strategy was to demonstrate that our lead product, NC-B8, is able to protect all neurons from degeneration, including motor neurons. So we first tested its effect in vitro [in cells] using mouse motor neurons," he says.

They discovered that NC-B8 was neuroprotective and the results were better than the impact of using riluzole or edaravone [existing MND drugs].

Following this initial discovery, the team tested whether NC-B8 could prevent neuronal cell death induced by Cerebrospinal fluid (CSF) taken from a person with MND, and the result was positive again. NC-B8 was also found to protect human motor neurons in cells (grown in the dish) from both healthy patients and MND patients.

When the team tested NC-B8 in vivo [inside a whole organism] of the SOD1 mouse model of MND, they observed that NC-B8 improved body weight, motor function and increased survival by simultaneously protecting neurons and muscle cells while repressing neuro-inflammation.

They also observed that NC-B8 treatment protected neurons and muscles from degeneration in canine degenerative myelopathy-diagnosed dogs, which is a canine disease very similar to MND. It is their goal now to demonstrate that NC-B8 has the same effect in humans.

Demonstrated efficacy

"What excites me the most about the antibody we are developing is that it demonstrated extraordinary efficacy. So far, whatever the neurodegeneration model we tested (MND, Parkinson's disease, Multiple sclerosis, Alzheimer's disease), whatever the stress that was faced by the neuron, whatever the species affected (mouse or dogs), it always demonstrated efficacy," said Dr Toulorge.

Dr Toulorge says that support *"from FightMND will enable us to perform regulatory toxicology studies that are required to begin NC-B8 clinical development."*

It *"will directly impact our ability to test NC-B8 in ALS (MND) patients. But more than that, we are now part of the FightMND army, which will give us additional strength to tackle MND,"* he adds.

FightMND has invested $970,000 in this research.

About Dr Damien Toulorge

Dr Damien Toulorge earned a PhD in Neurosciences in 2016 from the Université Pierre et Marie Curie, studying at La Pitié Salpetrière Hospital at the Paris Brain Institute. The hospital is known as the home of modern neurology, largely due to Dr Charcot, who practiced at the hospital and in 1865 was the first person to diagnose ALS (MND).

While studying for his PhD, Dr Toulorge worked on the neurodegenerative mechanisms at play in Parkinson's disease and tried to find new neuroprotective strategies. Following completion of his PhD, he worked as a scientific consultant and then as project manager at Pharnext, a French biotech developing compounds against neurodegenerative diseases, including MND.

In 2015 Dr Toulorge co-founded ENCEFA to pursue the development of therapeutics based on a new neuroprotective pathway that was discovered during his PhD studies.