Potential MND treatments move a step forward

By John Fox

Australian researchers are the first to discover how inflammation is triggered in motor neuron disease (MND) and identified the molecules involved, which could be the first step toward development of treatments to slow the progression of MND and possibly other debilitating neurological diseases.

Also known as Lou Gehrig's disease or amyotrophic lateral sclerosis, MND is a rare disorder that selectively affects motor neurons, severely impairing movement, breathing, swallowing and speech.

Currently incurable, MND is a rapidly progressive neurodegenerative disease, with an average life expectancy from diagnosis of just 3-5 years.

Most MND patients have an accumulation of TDP-43 protein in their central nervous system cells, which is now known to be associated with the inflammatory response preceding major MND symptoms.

"Although TDP-43 accumulation was known to be important in MND, our study is the first to link it to inflammation," said Seth Masters, an associate professor in the Division of Inflammation at Walter and Eliza Hall Institute of Medical Research (WEHI) in Melbourne, who co-led the study together with WEHI postdoctoral fellow Alan Yu.

In collaboration with scientists at the University of Melbourne and Melbourne's Hudson Institute, the researchers found that an immune sensor called stimulator of interferon genes (STING) was activated downstream of TDP-43, suggesting STING blockade might prevent inflammation, they reported in the October 8, 2020, edition of *Cell*.

"We showed this in several ways, most importantly by using cells from patients with MND due to mutations in TDP-43," Masters told *BioWorld Science*.

Recent work has demonstrated that TDP-43 did not just accumulate in the cytoplasm, but also moved into mitochondria, prompting the authors to take a more detailed look at the effects of TDP-43 accumulation in different cellular compartments. They showed that TDP-43 accumulation in the mitochondria triggered the release of mitochondrial DNA into the cytoplasm, where it activated the innate immune sensor cGAS/STING.

"There are some drugs that target downstream of STING, such as the Janus kinase (JAK) inhibitor ruxolitinib (Jakafi, Incyte), but these may not cross the blood-brain barrier [BBB].

"Therefore, in our study we used novel highly specific STING inhibitors, which can cross the BBB, but have never been tested in humans," he said.

"Fortuitously, our research team had already studied the role of STING in patients with rare mutations in the STING gene, who develop inflammatory disease early in childhood and we are now working out how to block this with

drugs other than JAK inhibitors," said Masters.

To this end, the research team used the highly specific new inhibitors to block the different components of this novel inflammatory pathway.

Using induced pluripotent stem cells (iPSCs) from patients with MND that can be cultured into motor neurons, they showed that STING blockade dramatically prevented inflammation and prolonged cell survival.

"Typically, these cells had about 20% reduced viability when we tested them, but we could rescue that back to the level of healthy control cells," Masters said. "This is an exciting first step before taking these inhibitors into the clinic for treatment for MND."

This research has also identified the activation of STING in people who had died due to MND.

"This information is useful, because we will now try and detect activation of the same pathway in patients who are alive," said Masters, noting, "it may be difficult if the levels are lower at an earlier stage of disease, but we will try."

Consequently, Masters and his team are now aiming to validate a neuroinflammatory biomarker of the pathway earlier in the disease progression.

Once such a biomarker has been discovered and validated, "we will better understand which patients will benefit the most from treatments targeting the pathway, so it may be possible to develop a treatment for MND patients," he said.

Interestingly, research in preclinical models has suggested that, although the anti-inflammatory drugs that inhibit STING did not prevent disease onset, they did slow the degenerative progression of disease by approximately 40%, offering hope for people newly diagnosed with MND.

"Hopefully this research could lead to treatments for people with established MND, who currently have few treatment options and a life expectancy post diagnosis of just 2-5 years," said Masters.

"While it isn't a cure, we hope it might extend life expectancy and dramatically improve the quality of life for people diagnosed with MND."

However, "while optimization [of putative STING inhibitors] continues in different pharmaceutical companies around the world, it is likely that some version of these will enter the clinic at some stage within the next year or two," said Masters.

"Then it will need to be demonstrated that the drugs are safe in healthy volunteers, before they can be tested in clinical trials in MND for example, and that will also take years," he predicted.

In this regard, "we will partner with industry to ensure that the first drugs targeting this pathway work in all of our preclinical models of MND and push for them to enter clinical trials against this disease as soon as possible."

Finally, such treatments might also be effective in slowing the progression of other neurodegenerative disorders, noted Masters.

"Eventually, we hope to develop a new class of STING inhibitors, not only to

stop the progression of MND, but also that of other neurodegenerative disorders including frontotemporal dementia and Parkinson's disease" (Yu, C.-H. et al. Cell 2020, 1833: 1).