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Over the last 24 months quite an encouraging amount of new information about the causes and contributing factors responsible for motor neurone disease (MND) has been uncovered. However, the cause of most cases of MND still remains a mystery.

Estimates have frequently placed the number of sporadic MND cases at around 90 percent of all cases (a new report suggests this is not accurate; see *MND Research Shorts*). It is therefore vital to be able to link the inherited, familial forms of MND to the apparently random sporadic cases. Although approximately 20 percent of all familial cases are associated to mutations in a gene called SOD1, recent research shows a group of related genes such as FUS and TDP-43 are associated with familial MND but may also be at least partly responsible for sporadic MND. This casts shadows on the role of SOD1 in MND and its possible importance in sporadic disease. This is important since most of the potential drugs for MND are tested on mice, and up until very recently the only MND mice carried the human SOD1 mutant.

This quarter sees a re-emergence of SOD1 back into the spot light with a report suggesting it may be important in sporadic MND pathology. In addition, an important link between TDP-43 and SOD1 is hinted at by recent research published in this quarter.

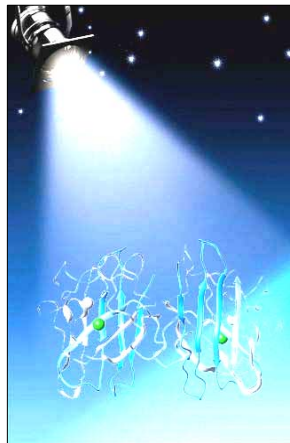
In this report we will look at these studies and some of the other MND research going on all around the world.

## SOD1 back in the spot light

Over the last couple of years the link between SOD1 and sporadic MND has taken a back seat with the discovery of TDP-43 mutations in some familial cases of MND and TDP-43 pathology present in a large proportion of sporadic MND cases. Scientists had previously looked for accumulations of SOD1 in sporadic MND, as can be found in familial MND associated with SOD1, but with the available tools were unable to find any.

Researchers from the University of Massachusetts, led by Professor Robert Brown Jr, have recently shown that with new molecular tools it is possible to detect an accumulation of SOD1 in a subset of sporadic MND patients. This important research then raises the question of how the mutations in SOD1 fit within an MND puzzle now seemingly dominated by genes such as TDP-43 and FUS that are functionally very different from SOD1.

Halfway across the globe, researchers from the National Institute of Neurosciences in Tokyo may have come up with part of the answer. In experiments akin to a molecular fishing trip, they reeled in mutant SOD1 and found that they also caught TDP-43. This means that there is an interaction between the gene products of these two important, but apparently unrelated, causes of MND. These observations are important because it means that any advances that are achieved by studying SOD1 models of MND are not limited to SOD1 associated MND.



## MND Research Shorts

- Researchers in Florida, USA have found that a toxin called BMAA can be found in local animals in levels that could affect human health. Researchers previously attempted to link this toxin to hot spots of MND such as in Guam.
- Scientists in Ireland have reanalysed recent data in an attempt to more accurately estimate the number of MND cases that are familial. The researchers estimate the familial versions of MND are more likely to be closer to 5% than the more commonly used estimate of 10% of all cases.
- The neurotransmitter best known for creating a feeling of happiness, serotonin, can also be found outside the brain in blood platelets. Researchers in France have shown that people with MND have lower levels of serotonin in their platelets, suggesting serotonin loss may be associated with MND.
- Researchers in Korea, have used bee venom to treat MND mice. It appears that in these mice bee venom reduced the inflammation associated with MND and provided a modest increase in lifespan.

## What is SOD1?

SOD1 is the abbreviation for superoxide dismutase 1. It is an enzyme that resides in every cell of your body, whose function is to scavenge harmful free radicals. In particular the toxic free radical called superoxide.

The SOD1 enzyme is produced from the instructions encoded in the SOD1 gene. Therefore mistakes, or mutations, in the gene translate to mistakes in the construction of the enzyme.

SOD1 can be found present in inclusions in MND affected motor neurones. Inclusions are accumulations of non-functional or damaged proteins (an enzyme is a type of protein). It is thought that the production of these inclusions may play a role in the demise of motor neurones in MND.

## Research suggests SOD1 may be a useful therapeutic

Recent work coming out of the University of Florida, USA, suggests that it may be worthwhile further investigating using the normal version of SOD1 as a therapeutic. The researchers found that the normal SOD1 could influence the toxicity of the mutant version. Meanwhile, research lead by Prof Julien in Quebec, Canada, has shown that increasing a molecule called chromogranin in cells increases the toxicity of mutant SOD1. This is interesting because the chromogranins are known to lead to a release of SOD1 from the cells in to the surrounding fluid. Once outside the cell the mutant SOD1 would be able to interact with a range of other cells and molecules that may also contribute to its toxicity.

With this in mind, the same researchers, this time lead by Dr Urushitani from Shiga, Japan, have studied the possibility of vaccinating against SOD1. The scientists modified normal SOD1 and injected it into MND mice. The vaccination significantly lengthened the lifespan of the MND mice.

Therefore, there is much work going on around the world that suggests that using or targeting SOD1 might be a possible therapeutic in the future.

## Glutamate pumps on the blink?

Glutamate is a vital neurotransmitter that is responsible for sending signals between many neurones in the brain. However, too much glutamate can be bad for neurones; the neurones can become 'overexcited' and die. Therefore, it is vital the glutamate that is sent out as a signal is removed once its job is done. Cells employ nano-pumps to pump any remaining glutamate back into the cell. It is thought that this process may be defective in MND.



Researchers in Baltimore, USA have shown that an inflammatory messenger, TNF-alpha, can result in reduced activity of the glutamate pump. This is notable because TNF alpha is found increased in MND patients and thus may contribute to cell death and dysfunction in MND. It seems other scientists at the Johns Hopkins University in the USA were thinking along the same lines because they screened 1,000 drugs for their potential to increase the efficiency of the glutamate pump. They found one drug in particular, harmine, was able to increase the levels of the glutamate pump and increased the uptake of glutamate in vivo. This is a promising lead that may become a treatment in the future.

## Disease progression in MND

MND is characteristically a progressive disease that seems to progress from nerves controlling one muscle group to the next. Scientists at the University Medical Centre in Utrecht in the Netherlands have shown that the amount of functional connections between dying neurones correlates to disease progression rate of MND. This study means that it is likely that the disease is progressing from neurone to neurone throughout the nervous system. In turn, this means that if we can target this process we may be able to stop MND in its tracks.

## Allergic reaction responsible for MND?

Researchers at the University of California LA have shown that a protein involved in allergic reactions, called IL-17, is increased in sporadic and familial forms of MND.



This protein is a molecule that normally responds to pathogens found in the body, but can be found acting inappropriately in allergic reactions such as asthma. This research raises the possibility that the body's immune system has gone a little haywire in MND and is contributing to cell death.

## Oxygen deprivation and MND

It has been hypothesised that deprivation of oxygen may be associated with MND. In fact, recent studies have suggested that occupations in which people are exposed to environments which result in oxygen deprivation or hypoxia may be a risk factor for MND. In Lille, France, scientists took white blood cells from MND patients and used them to examine the patients' ability to cope with oxygen deprivation. They found that, at the cellular level, MND patients had abnormalities in their response to hypoxia, or oxygen deprivation. This may explain the earlier findings that people with jobs involving deprivation of oxygen, such as firefighters, are more likely to get MND. There is still much work to be done to determine how these processes are linked to MND.

## Bone marrow transplants a possible treatment for MND?

Researchers in Israel have taken bone marrow from MND patients and injected them back into the same patient's spine. No major adverse effects were reported during follow-up. The patients' symptoms remained stable over the 6 months of study. While it is too early to suggest that using stem cells from one's own bone marrow is a viable treatment for MND, the researchers state that transplantation is a clinically feasible and relatively safe procedure. It is hoped that the cells, once transplanted, may modulate neuroinflammation in the brain and spinal cord.

