

## MND research in 2009

2009 is an exciting time to be involved in MND research. In the March 2009 International MND research update we reported recent discoveries of new genes that cause MND. This means we are one step closer to understanding this terrible disease. In this report we look at further studies that link SMN and SOD1 to these genes and another gene possibly related to MND called ANG. The fact that these newly found genes as well as the previously known SOD1 and SMN genes can be traced back to affecting the same processes gives us for the first time a common ground to start from. This means that MND research is now moving faster than ever, in laboratories all around the world, towards a better understanding and hopefully a cure for MND.



### MND Research Shorts

- *Researchers in Hokkaido, Japan have found a molecule in spinal fluid that may act as a marker for earlier detection of MND.*
- *Researchers from Boston, USA say that the treatment of MND with L-arginine shows promise after SOD1 MND mice lived 20% longer when treated before symptoms started and 9% longer when treated after symptom onset.*
- *Over one million people were asked about their exposure to chemicals over a 15-year period. Researchers found no significant link between ALS and exposure to most chemicals, including pesticides and herbicides.*
- *A research team in Basel, Switzerland has shown that some motor neurones are more vulnerable in MND than others. In vulnerable motor neurones a stress response coupled with a switching on of the brains immune system occurred in SOD1 MND mice and was followed by selective axon degeneration and spreading stress.*
- *Scientists in Korea have found that mutant SOD1 MND mice have increased zinc levels inside motor neurones compared to normal motor neurones.*

dysfunction. Thus, this important work suggests that SOD1 along with all other familial MND gene mutations found so far have some effect on a common process. In addition, the work suggests that supplementation of SMN might be a viable treatment for MND patients.

**RNA is a messenger molecule carrying all the information required to build a functional protein from the genetic blueprint in the DNA to the molecular machines that assemble functional proteins.**

### Another gene implicated in MND - with a similar function to TDP-43 and FUS!

The most recently found genes involved in MND (FUS/TLS and TDP43) are thought to be part of the molecular machinery that transfers information from the blueprint stored in DNA to the nano-factories that build functional proteins. Dr Seilhean at UPMC Université, France has found a mutation in the ANG gene in an MND patient. Of great interest is the fact that like other gene products recently found to be involved in MND, such as TDP-43 and FUS/TLS, it also plays a role in transferring genetic information needed to build proteins (RNA handling). This research further implicates these control processes in MND. If the faulty process is precisely identified this may lead to potential drug targets.

### SMN from spinal muscular atrophy, SOD1 and MND

A protein involved in spinal muscular atrophy, called 'survival motor neurone' (SMN), has previously been shown to be low in sporadic MND patients. A research team led by Dr Bradley Turner from the Howard Florey Institute in Melbourne has studied the role of the loss of the SMN protein in mice with mutant SOD1 associated MND. They found that the loss of SMN resulted in the shortening of MND mice lifespan. Amazingly the function of this protein is similar to that of FUS and TDP-43 in that it also processes and transports messenger RNA. It is very interesting to note that the results also show that mutant SOD1 induces mRNA processing

### A fly on the wall of TDP-43 MND research



The tiny fruit fly has joined the fight against MND. Fruit flies are estimated to share approximately 60% of the genes that make us human and have long been used as a tool to study the inheritance of genes. More recently fruit flies have been used as models of disease including Alzheimer's disease and now MND. Researchers from the

International Centre for Genetic Engineering and Biotechnology, in Trieste, Italy have studied the effects of eliminating the fruit fly version of the TDP-43 gene. Mutations in the human TDP-43 gene are associated with some forms of familial MND. The flies missing the

TDP-43 gene had a shorter life span and motor deficits. Since the flies without TDP-43 had MND-like symptoms the authors concluded that a loss of the function of TDP-43 is likely to be the cause of MND in families inheriting TDP-43 mutations. It is up to researchers now to try to precisely identify the function of TDP-43 that is required for healthy motor neurones.

### Overloading of electrical signalling in MND

The over-excitability of brain cells controlling our muscles has previously been observed in MND patients. Researchers from Rome, Italy led by Massimo Pieri aimed to determine if this over-excitability came about because of the processes happening inside each individual motor neurone or because of an interaction between motor neurones.

The researchers found that the individual SOD1 MND motor neurones from mice grown in a test tube showed dysfunctional electrical firing more often than that of normal mouse motor neurones. The research team say that this is the first time that overexcitability has been demonstrated in individual mutated neurones and that this opens up new prospects of understanding MND.

### Clinical trial

A team led by Dr Nefussy at the University of Tel-Aviv trialled the use of a drug called Granulocyte-colony stimulating factor (G-CSF) for treatment of MND. G-CSF is used to mobilise a sub-population of white blood cells from the bone marrow to the blood. G-CSF was found to be effective at mobilising cells into the blood. Although there was a trend of slowing disease progression following two G-CSF treatments by the end of the study the analysis showed there was no statistically significant benefit of the drug after six months.



### Motor neurone transport blockage

Motor neurones are the longest cells in the human body and can reach up to 1 metre in length. This causes a few transport problems for the cell as it must use a large amount of energy to power the transport of all kinds of molecules needed in the far reaches of the synapse. The neurone runs a highway of sorts carrying its



molecular passengers to the synapse. Dr Anna King and co-workers at the Menzies Research Institute in Hobart have found that in MND the long axons of the motor neurones have an unusual amount of blockages or traffic jams. The long axon of the motor neurone bulges and swells and the passage of important molecules is blocked. Eventually these blockages could be

detrimental to the neurones. Interestingly, the researchers found that it is the influence of cells in close proximity to the motor neurone that determine if there will be a blockage or not. The next exciting step will be to identify how the neighbouring cells cause the traffic jam.

*An axon is a long projection of a nerve cell, or neurone, that conducts electrical impulse away from the neurone's cell body.*

### Exercise and onset of MND

Due to reports of a higher than expected incidence of MND in professional sports people some researchers think there might be a relationship between rigorous exercise and onset of MND. A prime example of which is an unusually large proportion of MND in Italian soccer players. So far there is not enough evidence to say this is actually occurring in humans. Regardless, researchers in the UK headed by Professor Pamela Shaw have investigated the biological processes that occur when mice have undertaken extreme physical exercise. They found that in order for the mice to keep exercising a few molecular rearrangements needed to be made. In particular, the end of the motor neurones that communicate with muscles (synapse) needed to be able to adapt and change. Although there is no direct link between this study and MND the researchers say that this may have implications for MND since the junction between neurones and muscles are known to be susceptible to damage. They hypothesise that extreme exercise may be associated with the onset of MND in some cases.



### Do the genes fit?

In the last issue of this research report we noted that scientists hunting for variations in people's genetic makeup that affect sporadic motor neurone disease were coming back empty handed. More recently researchers have looked at DNA from almost 4,000 people to try to identify genes playing a role in MND. Although the team did not find any variations that could trigger MND they did find a gene that slowed the progression of the disease. Patients with a certain variant of the KIFAP-3 gene were found to have an increased survival of around 14 months. Interestingly the gene produces a protein that plays a role in transport of molecules along the long motor neurone highways (axons). The researchers hope that a further understanding of KIFAP-3 may lead to potential treatment targets.

