

**September 2009**

There are many fields of medical research ongoing around the world. Many people live in hope that this research can help them in some way.

One branch of science that spans many diseases or syndromes is what is called regenerative medicine. Regeneration of cells or tissues of the human body may eventually help heart attack victims, people who have severed their spinal cord and are paralysed, and also people with neurodegenerative diseases such as motor neurone disease.

At the forefront of this type of science are stem cells. In this report we look at the latest research going on around the world including a number of studies using stem cells. We also look at what a stem cell is. Lastly, we also take a look at what other MND science is going on around the world.

## **MND Research Shorts**

- *Researchers from Israel and Italy have worked together to show that drugs that mop up excess iron in the body can improve survival in MND mice.*
- *Copper and zinc deficiency affects the way that mutant SOD1 is formed. Researchers from the USA have shown that without copper and zinc the SOD1 protein is less stable and more likely to act inappropriately.*
- *Researchers from Japan have discovered that mutant SOD1 associated with some forms of familial MND interacts with and interferes with a protein called tubulin that provides "scaffolding" for the long motor neurone axons.*
- *Although lithium treatment was earlier shown to prolong life of SOD1 MND mice, a repeated study conducted in the USA has shown that treatment with lithium has no effect on MND mice lifespan.*
- *TDP-43 mutants have already shown to be associated with some forms of familial MND. Researchers in Australia have now shown that in some sporadic MND cases mutations in TDP-43 can be found further implicating it in MND.*

## **Stem cells and MND**

Embryonic stem cells are shaping up to be a promising tool for treating a range of diseases from heart disease to MND.

With this in mind a research group headed by Dr Ivan Velasco implanted embryonic stem cells that had been converted into motor neurones into rat spinal chords.

The stem cells were well tolerated in the rats, but although it looked like the implantation prolonged the start of symptoms it did not extend the life of MND rats carrying the human mutant SOD1. Interestingly, the implanted motor neurones had a much lower survival in MND rats compared to normal rats.

The researchers say that this result shows that the motor neurone disease environment is detrimental to grafted motor neurones in the long term. However, this kind of treatment may be best used in conjunction with other drugs in the future.



## **Loss of growth factor associated with motor neurone death**

The growth factor VEGF (Vascular Endothelial Growth Factor) is known for its ability to stimulate growth of blood vessels but is also known to promote the health and growth of neurons. Researchers in Michigan have looked at levels of VEGF in mice genetically modified to have motor neurone disease (SOD1 gene). They found that the levels of VEGF in MND mice were 50% lower than those in normal mice. The researchers then tested the effects of adding VEGF to motor neurones grown in the laboratory. They found that adding VEGF was protective against the toxic effects of mutant SOD1. These studies suggest that VEGF may be useful as a potential therapeutic tool for the treatment of MND.

## **What is a stem cell?**

Stem cells are a normal part of all tissues in the body. They are characterised by their ability to renew themselves and to convert into a range of specialised cell types able to perform specific functions. There are many types of stem cells in the adult body. Each of these are limited to the types of cells that they can create.

For example, in bone marrow there are stem cells that can make all of the cells in blood including white blood cells, red blood cells and platelets.

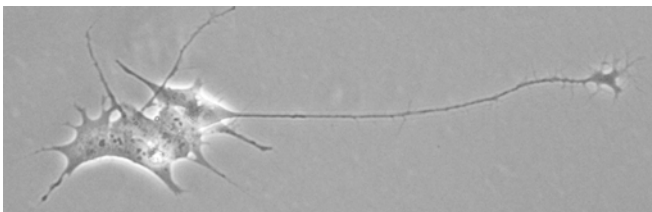
Embryonic stem cells are the most potent of the stem cells. They can develop into any one of the over 200 cell types of the adult body.

## Arming stem cells to fight MND

We saw earlier in this report that the growth factor VEGF may be a possible treatment for MND, we have also looked at research into stem cells. In this study researchers from Canada attempted to transplant neuronal stem cells that have been modified to produce large amounts of VEGF. Armed with their new VEGF weaponry the cells were transplanted into SOD1 MND mice. The cells were well tolerated and significantly delayed disease onset and prolonged survival of MND mice. The researchers say that their results suggest that a treatment involving transplantation of human neuronal stem cells genetically modified to over-produce growth factors might be of value in the treatment of MND patients.

## Bone marrow transplant; a potential MND treatment option?

Bone marrow transplants are a type of stem cell therapy. The stem cells that produce new blood cells are taken from the bone marrow of one individual and transplanted into another. This gives the recipient new stem cells that produce the cells that make up their blood, including white blood cells that fight infection and disease. It is known that the cells that function as the immune system in the brain are dysfunctional in MND. The precise mechanism by which this occurs has not been determined. However, researchers from Kansai Medical University in Osaka Japan have trialled bone marrow transplant as a potential therapeutic for MND in mice. The researchers took bone marrow from either normal or SOD1 MND mice for transplantations. The mice transplanted with normal bone marrow lived slightly longer than mice transplanted with SOD1 mouse marrow or non-transplanted mSOD1 mice. Importantly the normal marrow produced cells that found their way into the spinal cord and were found along side motor neurones. The authors suggest that this treatment may be useful in conjunction with other types of drugs yet to be discovered.



## Clinical Trials

### Training muscles to breathe easier

Professor Matthew Keirnan of the University of NSW led a research team that examined the effectiveness of a 12 week training program for MND patients aiming to strengthen the muscles that help us breathe in. The training regime had a high rate of compliance and after 12 weeks breathing capacity and other measures were tested. The researchers state that their results suggest that the 12-week programme has the potential to strengthen the inhalation muscles and delay progression of the loss of air intake in MND patients. This will now move on to Phase III trials.

## Nerve regeneration possible in MND?

It was once thought that nerve cells would not regenerate. Slowly this idea has been changing. In MND nerve cells that control motor function progressively die.

At the Okayama University Graduate School of Medicine researchers are examining the possibility that nerve cells lost during progression of MND can regenerate. In their studies they have found all the right signs to suggest that neurones are trying to regenerate in mutant SOD1 MND mice, but eventually the neurones give up and are all lost to the disease. The encouraging thing is that the regenerative capacity is present in the spinal chord so if a treatment is found, although it will not be possible to regain all muscle function, the remaining neurons may be able to regenerate.

## Taking out the trash

Within each and every one of our cells is a molecular machine that recognises and degrades broken down proteins. It is similar in concept to a garbage disposal unit. In MND, protein garbage piles up in the cell and causes all sorts of molecular sized problems. A protein named Dorfin has been known to



recognise and label junk protein to be mulched or degraded. Scientists from Nagoya University have studied the effects of increasing the amount of Dorfin in mutant SOD1 MND mice. Increasing the amount of Dorfin decreased the amount of SOD1 piled up in the cell and extended the lifespan of mice. This suggests that stimulating the cell to take out the trash and not letting the junk pile up may be an effective treatment of MND. Similarly, researchers from the University of Texas have shown that using a drug that stimulates one of the cells garbage disposal systems (called autophagocytosis) reduces the amount of accumulated TDP-43 in cells grown in the laboratory.

The accumulation of junk protein is also linked to a number of neurodegenerative diseases (not just MND) including Alzheimer's disease, Parkinson's disease and Huntington's disease. With this similarity in mind a group of scientists from the UK, Russia and Japan looked at the effect of the drugs Methyl Blue and Dimebon (in phase III clinical trials for Alzheimer's disease) on nerve cells grown in the laboratory. The treated cells had less accumulation of TDP-43 inside them suggesting that it may also be worthwhile trialling these drugs for the treatment of MND.