Research Update #5

ANOTHER STEP FOR STEM CELLS

A new effort is underway by researchers in Toronto and Vancouver to test the safety of an agent with potential for use in stem cell therapy for ALS.

Dr. Andrew Eisen, head of the ALS Clinic Vancouver General Hospital and the University of British Columbia, and Dr. Neil Cashman, head of the Neuromuscular Clinic of the Sunnybrook & Women's College Health Sciences Centre and the University of Toronto, are initiating phase 1 clinical trials to test an agent that activates stem cells.

The agent, known as granulocyte colony stimulating factor (G-CSF), causes stem cells in bone marrow to become activated and travel throughout the body - hopefully with a therapeutic effect.

"Our effort will be to find out if the treatment is toxic," says Cashman. While G-CSF has been used successfully for many years in treating a variety of conditions including heart attacks, multiple sclerosis and cancer, a theoretical risk exists when using this drug to treat ALS. The problem is the drug could stimulate microglial cells - immune cells that may be implicated in ALS. "Some authorities have argued that the cause of motor neuron cell death is activated microglial cells," explains Cashman, "so anything that has the possibility of activating these cells is something that we would use with great trepidation."

"There are many agents out there which cause stem cells to be activated and leave the bone marrow and go into the circulation. From a theoretical standpoint, the safest of these should be G-CSF. We've used this G-CSF in mice with ALS - transgenic mice - and it appears that there is no dramatic effect of worsening the disease. That gives us some confidence that we're on the right track for human patients."

The bone marrow stem cells have the ability to develop into various cell types, although where exactly these cells go, what they become, and how they might eventually be shown to be therapeutic is still unknown.

The Toronto study is pending ethics approval and the Vancouver study is already underway with no sign of toxicity so far. The trials, which were not industry-financed, were made possible through the Temerty Family Trust and the R. Howard Webster Foundation. "Their support has been very generous," says Eisen, adding there was no support from industry for the trials.

For safety reasons, only a few (less than ten) people can participate in each of the phase 1 trials. Eisen stresses that the trials are only a first step toward answering many questions about this type of potential therapy, and people should not feel left out. "We're not promising any miracles. If some miracle did occur, we would obviously open it up to the world."

Adult stem cells such as these bone marrow derived stem cells have the advantage that they come from the patient themselves, so they do not have the ethical complications of embryonic stem cells, and they do not pose the threat of rejection by the body's immune system and hazardous immunosuppressive drugs are not required.

Scientists led by Dr. Douglas Kerr at the Robert Packard Centre for ALS Research at Johns Hopkins recently achieved a big step for stem cell therapy when they successfully used agents to coax motor neurons from transplanted embryonic stem cells to migrate through the spinal cord in rats. When the motor neurons became impeded by the axon-inhibiting effects of the myelin around the spinal cord, the researchers applied a newly discovered chemical to block myelin's effect.

The agent worked, and some axons were able to extend their axons out through the spinal cord to reach nearby muscle targets. The researchers will now focus on ways of encouraging the motor neurons to reach even farther. The ability to direct the development and the migration of stem cells is critical to their future use in human therapies.

Dr. Freda Miller, stem cell researcher at the Toronto Hospital for Sick Children, made headlines in 2001 when she and collaborators discovered stem cells could be harvested from human adult skin. "Five years ago or so, what I would tell you is that there are only a few organs in your body that have adult stem cells and that the stem cells that are present in those organs only make cells that are specific to that organ. Somewhat to our surprise as a community, many more organs have stem cells than we ever thought, and those stem cells can perhaps do more things than we thought. They can make perhaps not just one cell type, but maybe a number of different cell types."

"There has been a sort of revolution in stem cell research in the last five or ten years," says Miller. "We as a community are now trying to take stem cells from an interesting biological phenomenon into the clinic."

Preliminary findings from the pilot trial have demonstrated safety of G-CSF in patients with ALS, although no therapeutic benefit was observed at the dose regimen used. Further studies are planned to optimize G-CSF treatment in mice before attempting human treatment trials.

By Lisa Beaton

ALS SOCIETY OF Canada - LA SOCIÉTÉ CANADIENNE DE LA SLA
265 Yorkland Blvd., Suite 300, Toronto, Ontario M2J 1S5
1 800 267-4257 www.als.ca