

STEM CELL RESEARCH AND ATAXIA

By Professor Bob Williamson, University of Melbourne

Every day, there's a new story about stem cells in the media. These stories include wild promises of medical miracles, together with gloomy predictions of the ethical disasters that may befall us. It is amazing that both the miracles and the disasters can be predicted in the same article! Neither of these extremes is true. Does stem cell research matter to those living with ataxia, and their families and friends? In this article I try to give the reality of stem cell science in relation to neurological disorders, and make some suggestions.

What are stem cells?

No living human has ever been cloned. Each one of us started as a one-cell embryo formed when a sperm fertilises an egg. This embryo is genetically unique, has about a one in four chance of making it to a foetus, and has a social context of belonging to a couple who want a baby. (Three in four embryos fail to make it; nature's way of dealing with some of the genetic mistakes that happen either in sperm, eggs, or early in development.) If the embryo survives, the single cell grows and divides and gives rise to every cell in our body.

Most of our cells are specialised: the nerve cells in the brain, for instance, and the 'epithelial cells' lining the lung. However, the early embryo is different. It is made up of 'stem cells', like the stem of a plant that gives rise to leaves, flowers and roots. A stem cell does not have a 'function' itself, but will turn into every kind of cell in the body.

We start our life as a collection of stem cells. As an embryo, and then a foetus, develops in the womb, these stem cells multiply, and a few stem cells branch off to form each of our specialised tissues, such as brain, lung, kidney, liver and skin. However, a few cells keep their unspecialised ('stem cell') properties. A newborn baby has lots of stem cells. As we get older, the number of stem cells falls, and their ability to form different cells seems to become restricted. In adults, although there are still stem cells, they have only a very limited ability to multiply to give a cell type other than their own. For instance, stem cells in the adult brain prefer to multiply to give new brain cells. It is difficult to convince them to become liver or lung cells.

Ethical issues

Stem cells that grow indefinitely, and can form any kind of tissue, can be obtained from very early human embryos (about a week after fertilisation). Many people feel uncomfortable about using human embryos in research, even if the embryo is composed of a few dozen cells and is the size of a pinhead. After all, the embryo could become someone like us! However, some embryos are available for research because they are 'left over' from IVF, if a couple is lucky and have the child or children they want quickly.

Most people agree that it is better to use 'left over embryos' for ethical research to treat a disease like ataxia, cystic fibrosis or Parkinson's than to throw them away. That is what Parliament in Australia decided in 2002 for embryos surplus to IVF programs. The same rule, roughly, applies in the United States (for most research), the UK, Singapore, and many other countries.

Obtaining stem cells

If stem cells are to be used to treat young people living with ataxia, there are two major problems to overcome. The first is that the cells have to be identical, or at least very similar, to those of the patient in their immune properties, or they may be rejected. Secondly, even though the brain and the dorsal root ganglia, the tissues most affected in ataxia, are not as likely to reject new cells as some other parts of the body, the cells will have a better chance of working well if they are from the patient or a close relative, not an 'unrelated embryo' or donor.

There are two possible ways around these problems, both of which are 'for the future'. The first is to use stem cells that are almost identical to the person with ataxia, but don't have the mutation. This could be done, for instance, by attempting to use cells from a brother or sister who has similar immune properties. Another source of cells would be cord blood from a baby whose brother or sister has ataxia. Cord blood is full of stem cells, and it has been shown that these stem cells can form neurons. There is one chance in four that the cord blood cells from an infant sibling will be identical in the major immune determinants, the so-called HLA system. However, there will still be minor differences, and it is not clear whether these will lead to cell death a few months after transplantation. Cord blood is safe to use; there have been thousands of cord blood transplants for patients with leukaemia and similar diseases.

The other approach is to transfer the DNA of a skin cell or blood cell from the patient into an egg (perhaps from the patient herself, or from her mother) from which all the DNA has been removed, and grow the egg until it resembles a hundred-cell embryo. (Most people, but not everyone, don't believe that this synthetic cell is similar to an embryo, unless an attempt is made to grow it in the womb.) This nuclear transfer technique is sometimes called *therapeutic cloning*, and is legal in the United States, Britain and most European and Asian countries, but not Australia.

This would give great stem cells that would not be rejected by the patient, but they would still carry the ataxia mutation. Clearly they would be useless if put in the brain or dorsal root ganglion - the mutation would have to be corrected first. We don't yet know how to do this, but groups in San Francisco, Rome and Melbourne are working hard on the techniques to make this happen.

Recent work

Recent experiments from Harvard University, reported in *Science* in August 2005, show that it may not be necessary to use a human egg to make a stem cell from a skin cell. Dr Kevin Eggan and his team showed that if you join a skin cell to an existing embryonic stem cell, it seems to 'wind the clock back', and the skin cell (which could be from a patient with ataxia) becomes able to mature into nerve or muscle cells. There is a lot of interest in these approaches in the UK, particularly in Newcastle University and Imperial College London.

There is no guarantee that the new stem cell techniques will solve the problems for people with ataxia, but I believe that stem cells represent a genuine hope for the future.

Bob has been a patron of Ataxia UK since 1991. As a human molecular geneticist who had worked on similar problems with cystic fibrosis, he was closely involved with starting Friedreich's ataxia research at St Mary's Hospital Medical School, University of London. With Sue Chamberlain, he set up the first group hunting for the Friedreich's ataxia gene in London in 1987, and located the gene to chromosome 9. In 1995 he moved to Melbourne, Australia to take charge of the Murdoch Institute, a research centre with over 600 staff devoted to studies of genetic disorders and child health. He continues to work on Friedreich's ataxia.

Ataxia UK will consider research proposals using stem cells. If you are a researcher interested in applying for a grant, email research@ataxia.org.uk for further information or visit www.ataxia.org.uk/page.builder/apply_for_funding.html

The Ataxian 154; 2006: 6-7

For more support or information please contact:

**Ataxia UK, 9 Winchester House, Kennington Park, Cranmer Road.
London SW9 6EJ www.ataxia.org.uk**

Helpline: 0845 644 0606 Tel: +44 (0)20 7582 1444 Fax: +44 (0)20 7582 9444 email helpline@ataxia.org.uk

We have a number of other publications on the ataxias available free of charge. In addition we publish a quarterly magazine called *The Ataxian* containing articles on research, living with ataxia and other relevant information. Our website also contains news of research projects.

Disclaimer

This leaflet is for information purposes only and, while every care is taken to ensure its accuracy, no guarantee of accuracy can be given. Individual medical advice should be sought before taking or refraining from taking any action based on the information contained in this leaflet and nothing should be construed as medical advice given by Ataxia UK or any of its officers, trustees or employees. No person shall have any claim of any nature whatsoever arising out of or in connection with the contents of this leaflet against Ataxia UK or any of its officers, trustees or employees.

June 2006