The promise of stem cells

Scarcely a month goes by without a significant piece of research into stem cells being published in a scientific journal. Each finding brings new insight into cell and tissue development and tantalizes the medical and scientific community with the possibility of repairing the ravages of age, trauma and a range of diseases from heart disease to Parkinson disease and diabetes. But how much of the reporting is hype and how much reality? Helen Gavaghan finds out.

In May last year, a US National Institutes of Health primer on stem cells claimed that research on stem cells "has the potential to revolutionize the practice of medicine and improve the quality and length of life". One year later, Dr Ron McKay, a leader in the field and now at the US National Institute of Neurological Disorders and Stroke in Bethesda, Maryland, has no doubt: "What has been happening during the past year is fantastic; it is mind boggling," he says, pointing out that clinical trials could begin within two or three years for treatment of heart disease and type 1 diabetes.

Just what is a stem cell and what makes it so medically versatile? The most basic definition is that it is a cell that can divide to give both another stem cell and a more specialized cell. It can be totipotent (able to form an entire organism), pluripotent (able to develop into most tissues of an organism) or multipotent (specialized for specific tissues, such as blood, skin, etc.). The three types are found at different stages of an organism's development and in different places in the body (see box).

Research into all types of stem cell holds promise both for a better understanding of human development and for curing disease. Totipotent cells, for example, led to the birth of Dolly the sheep and a subsequent raft of cloned animals. This work is giving an insight into embryo development. By working with pluripotent cells from embryos, which until the past year scientists believed was the only source of such cells, researchers have acquired a tool for exploring how cells differentiate to form specific tissues. With multipotent stem cells, researchers can study how they further differentiate to perform a specific job in an organ — how, for example, brain stem cells differentiate into neurons, that transmit information; into astrocytes, that nourish neurons; and into oligodendrocytes, that insulate neurons.

If, in studying stem cells, scientists gain a deeper understanding of normal development, they stand a better chance of being able to use these cells to prevent abnormal development. They can attempt to use the cells to create tissues to repair or replace damaged or aged tissue (since the 1960s, physicians have been using bone marrow transplants, consisting essentially of multipotent stem cells, to repair tissue damaged by cancer chemotherapy).

The stem cells that have caused the most stir are the pluripotent cells found in embryos. These stem cells have the potential to become any cell type and to provide a long-lived, stable culture, making them a potentially valuable medical resource for scientists wanting to generate specific tissues — from skin to brain or heart muscle.

For decades scientists have conducted basic research into developmental biology using the embryonic stem cells of rodents. Only now is the field of human embryonic stem cell research opening up.

Stem cells for diabetes

One piece of work in rodents that has the potential to treat type 1 diabetes in humans was published in *Science* at the end of April. Dr Nadya Lumelsky and her colleagues in McKay's laboratory successfully cultured from embryonic stem cells the islet clusters which form insulin in the pancreas. The amount of insulin these cells produced was low — only 2% of the normal amount — but McKay is confident that within a year this could be much greater. Researchers aim to test the procedure with human embryonic stem cells (in the US this work must currently be funded privately, because federal funds cannot be used for work on human embryos). Trials in patients with type 1 diabetes (the inherited form) are a real possibility within a couple of years, says McKay.

Though such work keeps alive the excitement over the potential of human embryonic stem cells, interest in adult stem cells is also mounting. Researchers have discovered that stem cells associated with

Stem cells — some basic notions

Embryonic stem cells are unspecialized or undifferentiated cells that can divide indefinitely in culture and can develop into specialized or differentiated cells. In the first few days after fertilization of an ovum, stem cells are totipotent, that is, they have the potential to become a complete organism, such as a human being. By about day four, the totipotent cells form a hollow sphere of cells, called a blastocyst (see photo), and have become a little more specialized. Pluripotent cells, that have a more restricted potential, make up the outer layer of the blastocyst and give rise to the placenta and other tissues needed to support fetal development. A second type of pluripotent cells form the so-called inner cell mass of the blastocyst and will give rise to most of the tissues in the body. These embryonic pluripotent cells are the stem cells of interest to science and medicine.

Pluripotent cells cannot generate a complete organism, but in normal development they do produce specialized, or multipotent, stem cells in the fetus or adult animal, which, in turn, produce the differentiated cells that make up the different components of the body.

The multipotent cells are the ones that some groups want to reprogramme and transform into different tissue types. This work is still at a very early stage and is producing very basic scientific information. Other groups take the tissue-specific stem cells and coax them along their path to full differentiation where they may become cells with therapeutic value, say brain cells for treating Parkinson disease or heart muscle cells for treating heart failure.

The current flurry of excitement over embryonic stem cells began with the publication of two papers in *Science* in 1998. Using techniques already developed in animals, two teams independently isolated and cultured human pluripotent stem cells from, respectively, embryonic stem cells and fetal tissue.

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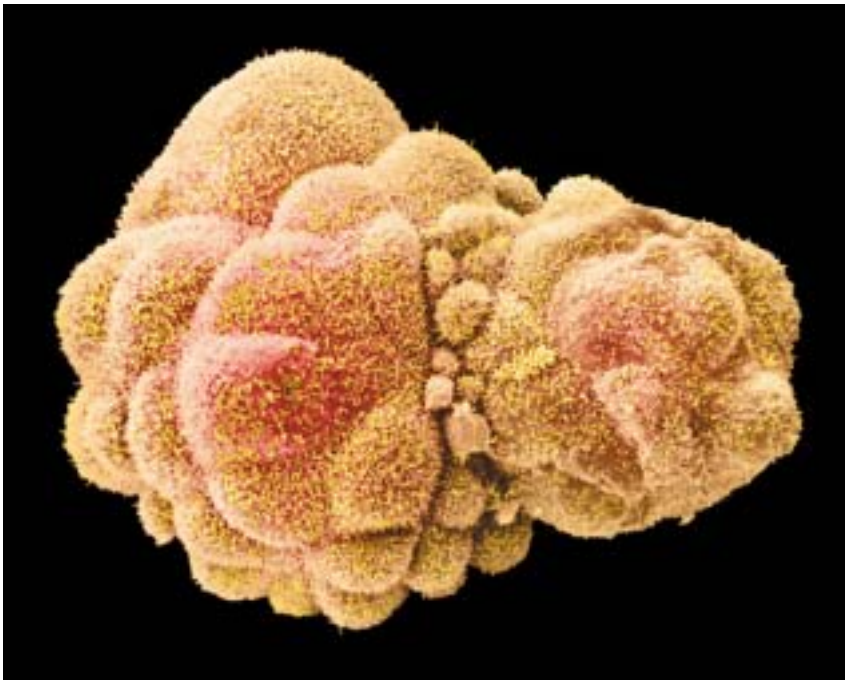

Dr Yorgos Nikas/Science Photo Library

Scanning electron micrograph of a six-day-old human embryo at blastocyst stage. The blastocyst, a partially hollow ball of cells, is composed of the outer cell layer and the inner cell mass, which forms the embryo proper. The inner cell mass is a source of pluripotent stem cells, that can develop into a multitude of different tissues and organs.

specific tissue types, say brain, can be "reprogrammed" to make muscle. This opens the possibility — still distant — that one could take stem cells from one part of a patient's body and reprogramme them to produce tissue grafts for damaged or degenerating tissue elsewhere, thus reducing the risk of rejection. Another possible route to this goal would be by using a procedure called Somatic Cell Nuclear Transfer (SCNT): the nuclei of adult stem cells isolated from an intended graft recipient are fused with an oocyte, or egg cell, from which the nucleus has been removed. The result is a totipotent cell, which can be used to form a blastocyst (see box and photo) *in vitro*, from which in turn embryonic pluripotent stem cells can be recovered and used to form graft tissue. This procedure has so far only been carried out in mice.

Complementary research

Those who oppose embryonic stem cell research on ethical grounds argue that the potential of adult stem cells, if realized, would obviate much of the need for embryonic stem cells. Dr Angelo Vescovi, a pioneer in this field and director of stem cell research at the San Raffaele Hospital in Milan, Italy, disagrees. He says that embryonic stem cell research looks at how the pluripotent cells gradually differentiate to become tissue-specific (or multipotent) stem cells, whereas research on adult stem cells looks at how they revert to a more primitive state before developing into new tissue. The two types of work are complementary, he says. The transformation of adult stem cells "shows promise, but we need to do a lot of rock-solid, steady work".

Dr Diane Krause from Yale University School of Medicine agrees that the two types of stem cell work are needed. She and her colleagues from several US groups have shown that bone marrow stem cells from an adult rat, if injected into rats that have had their bone marrow destroyed by radiation, are transformed into lung, gut, liver and skin cells, not only blood and bone-marrow cells. Yet, says Krause, scientists do not know how and why the bone marrow cells developed into such a wide variety of cell types. To find the answers, embryonic stem cell research is essential, she says.

For Dr Daniel Wikler, WHO senior staff ethicist, the ethical debate over such research is due to the fact that "embryonic stem cells lines cannot be established without the sacrifice of at least a few embryos". Some believe, he says, that embryos possess souls, or have a right to life, and maintain that killing any such being, even for the benefit of others, can never be justified. "But some who share this view still support the research because the embryos would not have lived in any case. Most, if not all, are surplus embryos received from fertility clinics, and the couples involved had directed the clinics to destroy them before being asked to donate them to science. The research is also generally supported by those who do not accept the premise that embryos created *in vitro* and not yet implanted in a woman's uterus have an inviolable moral status."

If an understanding of the reprogramming of multipotent adult stem cells is still a long way off and if the need for embryonic stem cell research remains controversial, the therapeutic potential of multipotent, or adult, stem cells is clearly promising. Perhaps their best-known medical application is the well-established practice of extracting from the bone marrow of cancer sufferers adult stem cells that are later transplanted back into the patients when cancer treatment has destroyed their bone marrow.

Further potential applications are in the pipeline. Researchers in both Vescovi's laboratory and McKay's, for example, can coax fetal brain stem cells into making dopamine-producing neurons which might be used to treat patients with Parkinson disease. In rodent studies to date, they have had a 30% yield, and currently the team is attempting to identify the best stage in the differentiation from brain stem cell to dopamine-producing neuron for implanting the neurons into the brains of rats with Parkinson disease. "We could see clinical trials in perhaps three years," he says.

While the scientists struggle to understand the basic science, the bio-pharmaceutical industry is showing an interest in the technology. "I think stem cells as a whole are extremely exciting," says Dr Michael Edwards, chief executive officer of ReNeuron, a London-based company working with brain stem cells from fetal tissue with a view to developing treatments for stroke. At a meeting of the British Association for the Advancement of Science last September, the company's chief scientific officer, Dr John Sinden, told delegates that the company expected to start phase I/II clinical trials by the end of 2001. "There is genuine potential in stem cells, but converting that potential to a product is not trivial," says Edwards. ■

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