

A scanning electron micrograph (SEM) showing several clusters of stem cells. The cells are spherical and covered in a dense network of fine, hair-like projections (microvilli) that extend into the surrounding dark space. The clusters are arranged in a somewhat vertical column, with some cells appearing more prominent than others.

STEM CELLS

MRC research for lifelong health

MRC

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A large, circular, out-of-focus microscopic image of a cell occupies the left half of the page. The cell has a bright, glowing nucleus in the center, surrounded by a lighter, textured cytoplasm. The background is a soft, light blue gradient.

MRC research: stem cells

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Introduction

The Medical Research Council (MRC) is dedicated to improving human health through excellent science. Funded by the UK taxpayer, our work ranges from molecular level science to public health research, carried out in universities, hospitals and a network of our own units and institutes. Our discoveries have benefited the health and wealth of millions of people in the UK and around the world. This booklet focuses on MRC-funded research into stem cells, including the exciting potential these have for repairing damaged body tissues and replacing them with healthy new cells. It also discusses challenges surrounding stem cell research and what the MRC is doing to address these, and gives an overview of regulation in the UK and worldwide.



About cells

Cells are the basic building blocks of all living things, including the human body – all of the different organs and tissues in our bodies are made up of different types of cells. The bulk of a human cell is made from a fluid called cytoplasm that contains the majority of its proteins and energy store. At the centre is the nucleus, which holds its DNA and directs the cell's function.

Throughout our lives, the cells in our body are constantly ageing, dying and being replaced through division of existing cells and growth of new cells. But this process can sometimes go wrong, particularly as we get older. Many human diseases, such as degenerative brain disorders, heart disease, diabetes and cancer, are due to things going wrong with cells.

So what are stem cells?

Stem cells are immature cells that can divide to produce more of themselves (self-renewal) or give rise to the specialised cells that make up our organs and tissues (differentiation). They are found in many places in the body and are present from just after fertilisation of an egg right through to adulthood. Unlike specialised cells, different types of stem cells can generate many different types of cell, such as the beating cells of the heart or the insulin-producing cells of the pancreas.

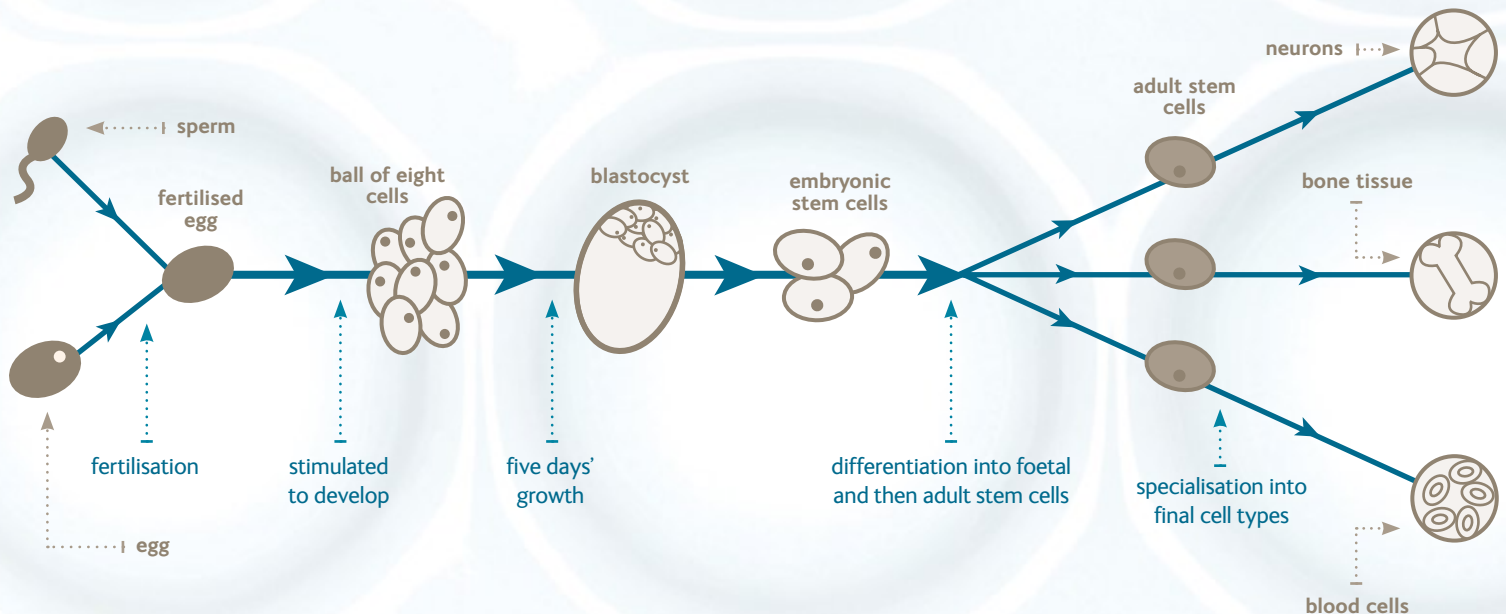
Scientists all over the world are studying stem cells to learn what makes them different from specialised cell types. They are also trying to understand what causes stem cells to renew themselves and what causes them to specialise into other types of cell. As the investigators learn more about these processes, they hope that it will become possible to collect stem cells and direct them to form particular types of cell from which to grow supplies of healthy tissue. This tissue could then be transplanted into people who are ill or injured to replace their own damaged cells and make them well again.

Embryonic stem cells

When a sperm cell fertilises a human egg, a one-cell embryo is formed. The fertilised egg then divides three times to make a ball of eight cells. These cells have the potential to develop into all of the different cell types that make up the human body, as well as those that form the placenta and umbilical cord. If the group of cells splits apart, two embryos are created and genetically identical twins begin to develop.

After about five days, the embryo consists of a ball of 50 to 100 cells called a blastocyst. It is about the size of one of the full stops on this page. The outer layer of the blastocyst forms the placenta and the inner part is made up of the 'inner cell mass', which can give rise to embryonic stem cells. At this stage the embryonic stem cells are pluripotent, meaning they are able to specialise into all the different types of tissue needed to form the human body.

Embryonic stem cells can renew themselves almost indefinitely, so once they are grown in culture, scientists can work with the same embryonic stem cells repeatedly.





Where do scientists get embryonic stem cells for research?

IVF treatment

The main source of embryonic stem cells is from surplus embryos donated by couples undergoing *in vitro* fertilisation (IVF). These would otherwise be destroyed.

Developed in the 1970s, IVF is used to treat couples who are having difficulty becoming pregnant. Usually, the woman takes fertility drugs to help her produce more eggs, and these eggs are harvested and fertilised with the man's sperm in a laboratory. The woman is then given hormone drugs before the fertilised eggs are implanted into her womb.

Some embryonic stem cells are derived from embryos that have failed 'preimplantation genetic diagnosis'. Also called embryo screening, this process is used sometimes to look for genetic diseases in embryos created by IVF, so that only normal embryos are implanted in a mother's womb. It might be carried out for couples who have a high risk of passing on an inherited condition, or to check IVF embryos for abnormalities in the number of chromosomes.

Somatic cell nuclear transfer

Somatic cell nuclear transfer (SCNT), also called therapeutic cloning, has the potential to create copies of a patient's healthy cells to replace or repair damaged or diseased tissues and organs. SCNT involves removing the nucleus from a donated egg and fusing this 'empty' egg with one of a patient's healthy cells. The egg-cell combination is then stimulated to develop into a blastocyst, from which embryonic stem cells can be extracted after five days of growth.

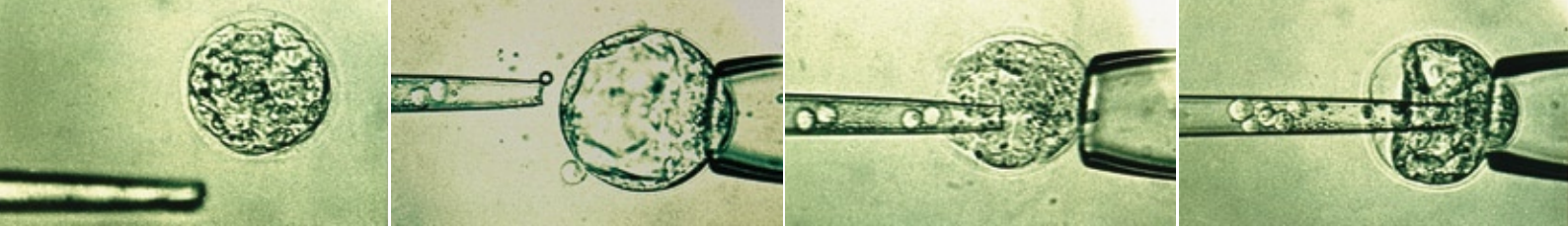
If the patient suffers a genetic disease (such as cystic fibrosis), the resulting embryonic stem cells could not be used for cell-based therapy unless the genetic problem could be corrected first. But they could be used to study the disease in the lab, and perhaps find other types of therapy such as new drugs.

Human admixed embryos

Human admixed embryos are a type of SCNT. Scientists are exploring the possibility of creating embryos by transferring the nuclei of human cells into animal eggs that have had almost all their genetic material removed. They hope that this will provide a good source of stem cells and will address the limitations imposed by the shortage of human eggs to use for SCNT. In late 2007 the Human Fertilisation and Embryology Authority granted licences to two teams of researchers to create human admixed embryos.

Induced pluripotent stem cells

In 2006, researchers found a way to reprogramme mouse skin cells and turn them back into cells very similar to embryonic stem cells. A major breakthrough was achieved in 2007 when researchers also achieved this in human cells, opening up a possible new source of pluripotent stem cells, but without the need to use actual embryos. This technology is at a very early stage and the techniques used to provide the necessary reprogramming require genetic modification and cannot currently be used to develop therapies. Nevertheless, scientists anticipate making rapid progress towards better understanding and refining approaches to generate these cells. The short-term goal is to use them to help model human diseases in the laboratory.



Foetal stem cells

Foetal stem cells are needed for a foetus to grow and mature. They have matured part of the way towards becoming fully differentiated adult cells but not as far as adult stem cells. However there are ethical issues around obtaining foetal tissue for research, and difficulties with obtaining large quantities of foetal stem cells.

Adult stem cells

The term adult stem cell can be misleading. In fact, so-called adult stem cells are found in adults, children and babies, and even in the umbilical cord.

As an embryo develops, embryonic stem cells specialise into the different cells that make up the body. The genes needed for earlier stages of development are switched off at various points along the way until only those needed for a single function remain active. For example, stem cells that specialise into muscle cells eventually lose the ability to do anything else.

Adult stem cells can be derived from embryonic stem cells that have only partially specialised. So they retain the ability to generate a limited number of cell types but can no longer make all of the different cells in the human body. Adult stem cells persist in many tissues, such as the bone marrow, blood, eye, brain and skeletal muscle. Their job is to replace and replenish cells that are continually lost by depletion and damage. For example, blood-forming adult stem cells in the bone marrow are able to generate the three different cell types that make up the blood. Adult stem cells can also be obtained from the umbilical cord or placenta at birth. Like other adult stem cells, these stem cells are able to generate some but not all types of human cells.

Which type to use

Embryonic stem cells are able to develop into many more different cell types than adult stem cells and it tends to be easier to control their specialisation and growth. They are also easier to isolate than many adult stem cells. On the other hand, a patient's own adult stem cells could be used to treat a disease without their body rejecting them as it might reject embryonic stem cells from a donor. Early indications suggest that induced pluripotent stem cells have similar properties to embryonic stem cells, offering the possibility of their future use once technological hurdles have been overcome. Because of the advantages and disadvantages of the different types of stem cells, scientists continue to research them all in the quest for medical advances and new treatments. And information generated on one type of stem cell often informs research into the other.

- » **PLURIPOTENT:** The embryonic stem cells that scientists work with are usually pluripotent. This means that they have the ability to form all of the different cell types that make up human organs and tissues, as well as sperm and eggs.
- » **MULTIPOTENT:** Stem cells that have already partially specialised into a particular broad cell type, but can still differentiate into different types within that. For instance, blood-forming stem cells can specialise into red or white blood cells or platelets, but cannot generate brain cells.
- » **UNIPOTENT:** Partially specialised stem cells that can form only a single type of cell, such as stem cells in the testis that go on to produce sperm cells.

A microscopic image showing a dense cluster of cells. Some cells are highlighted with bright green fluorescence, while others show orange or yellow fluorescence. The background is dark, making the glowing cells stand out. The overall texture is granular and complex, typical of a cell culture or tissue section.

Stem cells and your health

Many diseases are caused by the premature death or malfunction of cells. For instance, Parkinson's disease is due to brain cells dying, while type 1 diabetes is caused by faulty pancreatic cells. Scientists believe that stem cell therapy may offer a revolutionary way to treat such conditions by repairing diseased body tissues and replacing them with healthy new cells. But it is important to remember that a huge amount of scientific study is still needed. Researchers don't yet understand exactly how stem cells work. To be able to release their potential, they must first learn how to direct stem cells to become, for example, muscle cells for damaged hearts or neurons to treat brain diseases. Scientists also have to learn how to make sure that stem cells do not multiply in an uncontrolled way and create tumours.

Existing stem cell therapies

For many years, patients with blood diseases such as leukaemia have been treated by having healthy adult stem cells transplanted into their bone marrow to replace diseased cells that are killed off by chemotherapy. The aim is to integrate the healthy cells into the patient's body so that they begin to function on their own. Bone marrow stem cell transplants are possible because the large numbers of stem cells required can be accessed in the body relatively easily, unlike many other types of adult stem cell.

Adult stem cells may also be important in skin grafts to treat serious burn victims and to grow new corneas for people with impaired vision, as well as possible benefit in other conditions. However, further research into these therapies is needed before they can be used more widely.

Stem cell milestones

Scientific

1957

First successful intravenous infusion of bone marrow in patients receiving radiation and chemotherapy, Mary Imogene Bassett Hospital, USA.

1978

First IVF baby born, following fertilisation of human eggs outside the body by scientists at Cambridge University, UK.

1981

Successful cultivation of mouse embryonic stem cells by Sir Martin Evans at Cambridge University, UK, and Gail Martin at the University of California, USA.

1996

A sheep is cloned using cell nuclear replacement at the Roslin Institute, Edinburgh University, UK.

1998

First human embryonic stem cell lines are created at the Wisconsin Primate Research Center, USA.

2003

Researchers generate the UK's first human embryonic stem cell line, King's College London, UK.

UK Regulatory

1982

The Warnock Committee is formed to examine the moral questions surrounding assisted reproduction and embryo research.

1984

The Warnock Report backs human embryo research into reproductive-related areas but advises tight regulation.

1990

The Human Fertilisation and Embryology (HFE) Act is passed.

1998

The HFE Authority and the Human Genetics Advisory Commission recommend that somatic cell nuclear transfer (SCNT; see page 5) is investigated for therapeutic purposes but not for reproductive cloning.

2000

A report by the Donaldson Commission recommends that research using human embryos (created by IVF or by SCNT) to increase understanding of human disease and disorders, and their cell-based treatments, should be permitted subject to the controls in the 1990 HFE Act.

2001

HFE Act amended to allow research on embryos for the purposes of increasing knowledge about the development of embryos, increasing knowledge about serious disease, and enabling such knowledge to be applied to developing treatments. Parliament introduces additional legislation prohibiting reproductive cloning.

2002

A House of Lords Select Committee concludes that stem cells have great therapeutic potential and that research should be conducted on both adult and embryonic stem cells.

2002

A Steering Committee, chaired by Lord Naren Patel, is set up to oversee the development of a UK Stem Cell Bank and to establish codes of practice for the use of human stem cell lines.

2003

Chinese researcher Hui Zhen Sheng creates a new source of embryonic stem cells by fusing human cells with rabbit eggs.

2003

Teams led by Austin Smith at the Institute for Stem Cell Research in Edinburgh and Robin Lovell-Badge at the MRC National Institute for Medical Research in London show that proteins called Oct-4, Sox-2 and Nanog are essential for stem cells to retain their ability to turn into almost any cell type and to self-renew.

2007

The International Stem Cell Forum publishes the results of a study characterising 59 stem cell lines, which will help to ensure that future stem cell research involves internationally co-ordinated quality standards.

2007

Teams of researchers at Cambridge and Oxford Universities independently discover a new type of stem cell in mice and rats that is very similar to human embryonic stem cells.

2007

Two independent teams of researchers – at Kyoto and Wisconsin universities – produce human induced pluripotent stem cells. These are thought to be very similar, if not identical, to embryonic stem cells but are made by reprogramming an adult cell (see page 5).

2002

The UK Stem Cell Bank, funded by the MRC and the Biotechnology and Biological Sciences Research Council, is initiated at the National Institute for Biological Standards and Control (see page 13).

2003

The International Stem Cell Forum (ISCF) – initially made up of nine funders of stem cell research from around the world including the MRC – is established to encourage international collaboration and funding support for stem cell research (see page 13).

2004

The ISCF begins a review of global ethics and regulation relating to stem cell research.

2005

The UK Government sets up the UK Stem Cell Initiative, with the aim of working with the public and private sectors to draw up a 10-year vision for UK stem cell research.

2006

The Human Tissue Act 2004 and Human Tissue (Scotland) Act 2006 come into force. The Human Tissue Authority regulates the storage of all cells for human application across the UK, as one of the competent authorities under the EU Tissue and Cells Directive.

2006

The Biotechnology and Biological Sciences Research Council leads the research councils and relevant government departments in establishing a UK National Stem Cell Network to encourage links between researchers and to encourage development of an integrated national stem cell research community.

2007

The UK Government publishes a bill allowing the creation of human admixed embryos by fusing human DNA with animal eggs to create embryonic stem cells for research.

How is stem cell research regulated?

- » Human reproductive cloning is illegal (and carries a jail sentence) in the UK.
- » Any research involving human embryos must be licensed by the Human Fertilisation and Embryology Authority.
- » Embryonic stem cell research is allowed, but cells may only be obtained from donated embryos left over from *in vitro* fertilisation or created by somatic cell nuclear transfer (see page 5).
- » Embryos may only be used for research until they are no more than 14 days old.
- » Research involving embryos must be to increase understanding and find treatments for serious diseases or for fertility research.
- » Researchers granted a licence to derive new embryonic stem cells should deposit a sample of any stem cell line they create in the UK Stem Cell Bank, which will make stocks of the cells available to the international research community.

UK stem cell regulation

In the UK, the Human Fertilisation and Embryology (HFE) Authority regulates all embryonic stem cell research under the 1990 HFE Act. The Act states that all research involving embryos must be granted a license for one of the following purposes:

- » Promoting advances in the treatment of infertility.
- » Increasing knowledge about the causes of congenital diseases.
- » Increasing knowledge about miscarriage.
- » Enhancing knowledge in the development of more effective contraception.
- » Detecting genetic or chromosomal abnormalities before implantation.

In response to the cloning of a sheep (Dolly) at the Roslin Institute in Edinburgh in 1996, the HFE Authority formed a Human Genetics Advisory Group. This group recommended that embryo research should be allowed to develop therapies for diseases affecting the mitochondria – the 'power houses' of cells, which process oxygen and turn food into energy – and to develop treatments for diseased and damaged tissues and organs. It deemed human reproductive cloning unacceptable. In 2000, a Department of Health expert committee chaired by Chief Medical Officer Sir Liam Donaldson recommended that research on embryos – both surplus embryos left over from IVF treatment and those created by somatic cell nuclear transfer – should be permitted to increase understanding of human diseases and disorders and of their cell-based therapies.

Based on these developments, the HFE Act was amended in 2001 to include the following additional purposes for which research licenses may be granted:

- » Increasing knowledge about the development of embryos.
- » Increasing knowledge about serious disease.
- » Enabling any such knowledge to be applied in developing treatments for serious disease.

At the end of 2002, a Steering Committee was set up to oversee the development and operation of the UK Stem Cell Bank and to develop codes of practice for the use of human stem cell lines. Chaired by Lord Naren Patel, the committee is made up of experts from a range of fields, including obstetrics, surgery, clinical embryology, bioethics, theology, law, stem cell research and sociology.

In 2008, the UK Parliament approved a bill updating the 1990 HFE Act. The bill permits the creation of embryos by fusing human DNA with animal eggs, which could provide a new source of stem cells for research. It also upheld previous restrictions on stem cell research, including the 14-day limit on working with embryos.

Stem cell regulation worldwide

Globally, stem cell research is becoming increasingly important, with many countries investing heavily in this area. Although international collaboration is desirable, this can be problematic since the regulatory framework surrounding human embryonic stem cell research varies considerably between countries. A number of countries have similar regulations to the UK, such as Australia, Israel, Japan, Singapore and Sweden. Others, including Canada, France and the Netherlands allow research using embryos left over from IVF programmes, but do not permit somatic cell nuclear transfer using human cells (see page 5). Stem cell research is more restricted in Italy, Germany, Poland, and Portugal. The situation is even more complex in the USA, where the Federal Government is more restrictive in its approach than many individual states, with some now adopting policies equivalent to the UK position, but many having no regulations.



Supporting stem cell science worldwide

The UK is a world leader in stem cell research and the MRC has played a major part in this achievement. We had a key role in setting up the International Stem Cell Forum (ISCF), which encourages international collaboration and funding support for stem cell research. And in 2004 we played a lead role in setting up the UK Stem Cell Bank. The world's first international stem cell bank, this is an important facility accessible to scientists in the UK and around the world.

The International Stem Cell Forum

The ISCF has three key projects. The first is the International Stem Cell Initiative (ISCI) led by Professor Peter Andrews of the University of Sheffield Centre for Stem Cell Biology. The ISCI is developing an internationally-agreed set of rules for working with human embryonic stem cells. In June 2007 the group published the results of research into 59 cell lines, revealing how particular lines vary under diverse growth conditions and when grown by different laboratories. A wide range of information for each of the cell lines is freely available in a registry on the ISCF's website.

Second, a global review of ethics and regulation of stem cell research has been carried out by the ISCF Ethics Working Party. The group, led by the forum's Canadian member organisation, includes ethicists, research scientists, clinicians and lawyers from the forum's members. Together they have reviewed the different ethical issues and regulations in countries that fund stem cell science, with a particular emphasis on research involving embryonic stem cells. The aim was to identify best practice guidelines for stem cell research and to develop a global register of clinical trials involving stem cells. The results of this work are also available online.

A third project is the ISCF stem cell banking initiative. Led by the UK Stem Cell Bank (see below), this aims to coordinate and harmonise international stem cell banking and help address barriers to the development of clinical-grade stem cell lines given the differing approaches to therapeutic licensing worldwide.

You can find out more about all of these projects at www.stemcellforum.org.

ISCF MEMBERS

- » **Academy of Finland**
- » **Australian National Health and Medical Research Council**
- » **Californian Institute of Regenerative Medicine**
- » **Canadian Institute of Health Research**
- » **Chinese Academy of Sciences**
- » **Czech Science Foundation**
- » **Danish Centre for Stem Cell Research**
- » **Deutsche Forschungsgemeinschaft, Germany**
- » **INSERM, France**
- » **Instituto de Salud Carlos III, Spain**
- » **Israel Academy of Science and Humanities**
- » **Italian National Institute of Health**
- » **Juvenile Diabetes Research Foundation International**
- » **Medical Research Council, UK**
- » **National Institutes of Health, USA**
- » **Netherlands Organisation for Health Research and Development**
- » **RIKEN, Japan**
- » **Singapore Biomedical Research Council**
- » **Swedish Research Council**
- » **Swiss National Science Foundation**
- » **Yonsei University College of Medicine, South Korea**

UK Stem Cell Bank

The UK Stem Cell Bank opened in 2004. It was a joint initiative between the MRC and the Biotechnology and Biological Sciences Research Council. The first of its kind in the world, the bank is responsible for storing, characterising and supplying ethically-approved, quality-controlled stem cell lines for medical research and treatment. It is located at the National Institute for Biological Standards and Control (NIBSC), a publicly-funded organisation whose job is to assure the quality and safety of biological medicines, such as vaccines and blood products. The NIBSC works closely with the World Health Organization to store and distribute samples that are used to control the quality of biological medicines around the world.

The UK Stem Cell Bank is a repository for human stem cells derived from adult, foetal and embryonic tissues and is open to scientists in the UK and abroad. It operates under a strict code of practice approved by a high-level steering committee. The UK's first two human embryonic stem cell lines were approved for deposit in the bank in May 2004. As of March 2008, 65 lines had been approved for banking – derived both in the UK and overseas – and the bank aims to add around 12 more stem cell lines each year. The bank has established an international profile for developing the best ways to bank stem cell lines for research and therapy, and actively supports national and international research and training programmes.

Research by MRC scientists

MRC researchers around the UK are carrying out a wide range of stem cell research. In the future, their work may result in new therapies for people with all sorts of diseases, such as those affecting the:


- Central nervous system
- Major organs
- Eyes
- Blood
- Muscles
- Skin
- Bones

Sir Martin Evans, known as the “father of embryonic stem cell research”, shared the 2007 Nobel Prize in Physiology or Medicine for his work introducing specific gene modifications into mice using embryonic stem cells. This work paved the way for targeted manipulation of genes and experimental mammalian genetics – everyday tools used by scientists to improve understanding of the influence of genes on disease. Sir Martin was supported by the MRC between the 1970s and 1990s.

Early embryos

MRC researchers around the UK are carrying out pioneering research into both embryonic and adult stem cells, including what determines the type of cell they become and how to direct this process. This spans work aimed at defining the best conditions for isolating and maintaining stem cell cultures, as well as research aimed at identifying factors that cause cells to divide and self-renew or to specialise into other cell types.

Our scientists at the Scottish Centre for Regenerative Medicine in Edinburgh have shown that a protein called Mbd3 is crucial for embryonic stem cells to specialise, for example, by forming brain or skin cells. The team made mouse embryonic stem cells that lacked the Mbd3 protein and found that they failed to form specialised cell types as they were supposed to. When injected into an early mouse embryo, the cells behaved in a similar way, disrupting its normal development. Lead researcher Dr Brian Hendrich said: “It is well established that embryonic stem cells need certain factors to self-renew. We have now shown, for the first time, that to leave that state and go down the specialisation pathway, cells require the activity of Mbd3.”



MRC-funded scientists discovered a new type of embryonic stem cell in mice and rats which is very similar to human embryonic stem cells. The team, led by Professor Roger Pedersen at Cambridge University, found that when mouse stem cells were derived from the innermost cell layer of a one-week-old embryo rather than from the usual three-to-four day-old stage, they resembled human embryonic stem cells and had many of the same properties. The discovery was made simultaneously by an Oxford University team in collaboration with scientists at the US National Institutes of Health. The research is likely to accelerate understanding of stem cell development and lead to better models of human disease. “Our hope is that pinpointing the developmental stage when human embryonic stem cells originate will help scientists who are using stem cells to develop cures for injuries and disease,” said Professor Pedersen.

Clinical grade research on embryonic stem cells

Before stem cells can be used to treat patients, they must meet strict quality standards called Good Manufacturing Practice (GMP). In 2004 the UK Stem Cell Bank set up the first clinical grade GMP facility for human stem cell banking in the European Union.

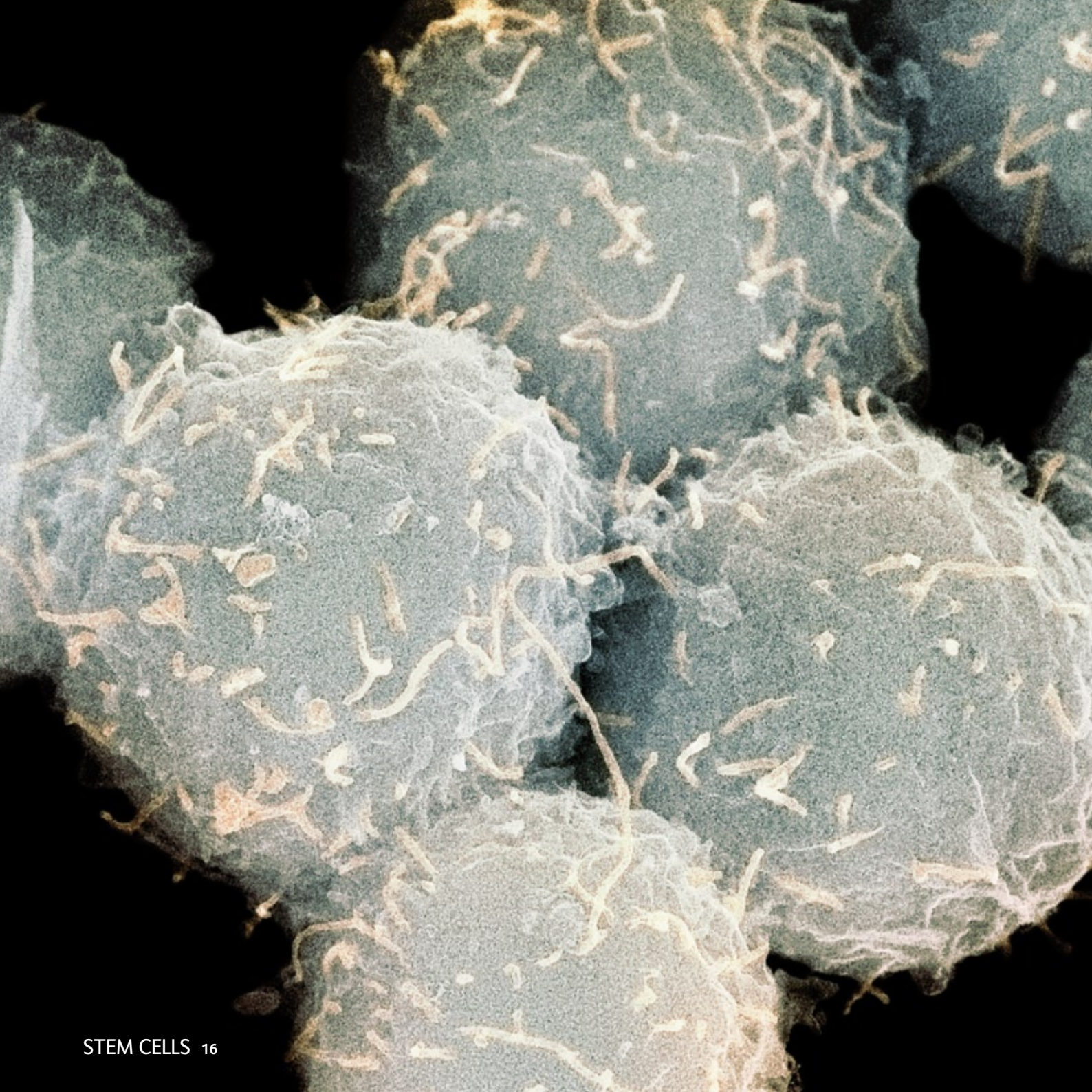
This was followed in January 2006 by the opening of the UK’s first GMP laboratory for the derivation of clinical grade human embryonic stem cell lines, at the Centre for Stem Cell Biology at Sheffield University. Professor Harry Moore, co-director of the centre, said that the laboratory “will enable the University of Sheffield to continue to work at the forefront of global stem cell research into regenerative medicine, which is paving the way for an international revolution in health care.”

The MRC has also provided funds to laboratories in Birmingham, London, Manchester and Newcastle to upgrade to GMP standard, enabling them to also generate and work with clinical-grade embryonic stem cells that can be used to treat human diseases.

Modelling human diseases

Researchers at the MRC Molecular Haematology Unit in Oxford and the Centre for Regenerative Medicine in Scotland genetically modified a mouse to study the blood disorder alpha thalassaemia. People with the condition have a shortage of alpha-globin protein, which is a crucial component of the oxygen-carrying molecule haemoglobin in red blood cells. As a result their blood cells cannot transport enough oxygen around the body, causing some carriers to be severely anaemic. The team replaced the mouse alpha-globin gene with a human version, so the animal produces the human form of the protein. Professor Doug Higgs, Director of the MHU, said: “At present much of our understanding of human genetics relies on mouse models. This work represents an important step forward in producing more authentic models of human genetic disease.”

Researchers have also used embryonic stem cells to create the first mouse model of human Down syndrome. Down syndrome is a genetic condition caused by the presence of three copies of chromosome 21 instead of the normal two – known as an ‘aneuploidy’. In a study co-funded by the Wellcome Trust, a team led by Dr Victor Tybulewicz of the MRC National Institute for Medical Research and Professor Elizabeth Fisher of the Institute of Neurology, University College London, inserted a copy of human chromosome 21 into mouse embryonic stem cells and used these cells to generate a mouse carrying the extra chromosome. The mouse had similar problems to those that can occur in people with Down syndrome, including problems with its memory, brain function and in the formation of its heart. “Aneuploidies are seen in at least five per cent of all pregnancies and are therefore a big cause of human illness, death and miscarriage,” said Dr Tybulewicz. “This technology will provide a crucial genetic tool in understanding this complex human syndrome.”





Replacing blood

Human blood is made up of different types of cells that each have different functions. For example, red blood cells carry oxygen around the body while white blood cells protect us against infections. As blood cells die they are replenished from a pool of cells known as 'haematopoietic', or blood-forming, stem cells. These are found in the bone marrow and have the capacity both to self-renew and to generate all the different types of blood cell.

Scientists at our Molecular Haematology Unit (MHU) in Oxford are working to establish a complete genetic and molecular description of how blood stem cells form in a developing embryo and behave in the adult. Because blood cell development is similar in all animals with backbones, the scientists are studying two primitive animals with backbones – the *Xenopus* frog and the zebrafish – in the hope that these will provide insights into human development.

Also at the MHU, Dr Rajeev Gupta discovered a link between a gene and human blood cell activity, giving hope that the success of stem cell transplants could be improved for blood cancer patients. The gene, known as *Nov*, plays a key role in regulating the production of blood from stem cells by making a hormone-like protein. The discovery may lead to *Nov* or a related gene playing a clinical role in stem cell transplants in the future.

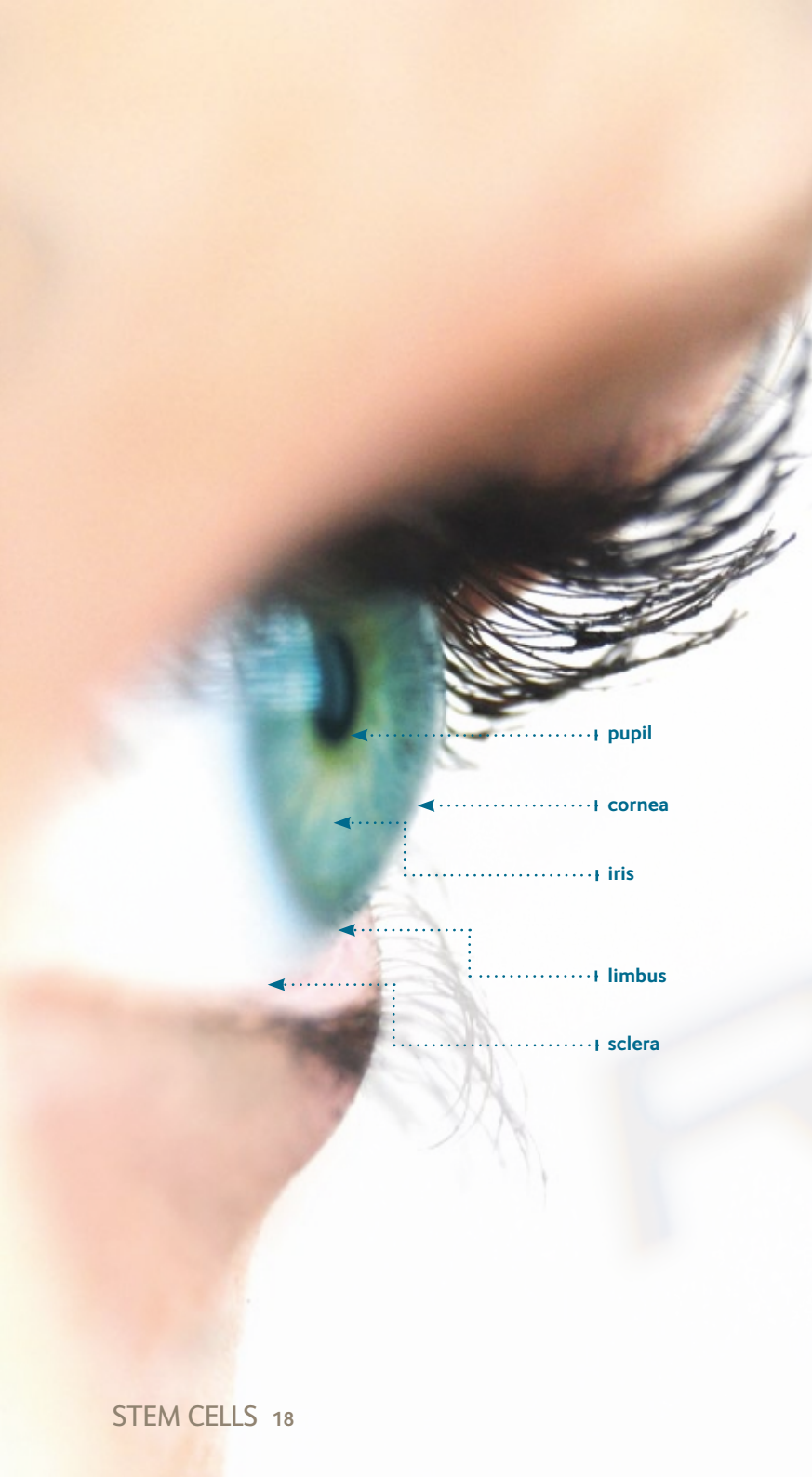
Repairing the brain and central nervous system

Stem cells may offer hope to patients with brain and central nervous system diseases and injuries. In conditions such as Alzheimer's and Parkinson's, nerve cells in the brain die, so replacing these cells using stem cells could help sufferers in the future. Patients with Alzheimer's disease have many different types of cell dying at random in their brains, which results in a gradual decline in mental function and memory. But in patients with Parkinson's disease, only cells in a part of the brain called the substantia nigra die, causing a loss of control of body movement.

Professor Steve Dunnett and colleagues are working on developing neural cells for future transplantation into patients with Huntington's and Parkinson's diseases. Their efforts are based on using embryonic or germ line (egg or sperm) cells or a type of foetal cell to provide reliable and renewable sources of neurons, with the aim of restoring brain function.

At the University of Nottingham, Professor Philip Bath has discovered that bone marrow stem cells may be able to repair the damage done to the brain by a stroke. Many patients lose the ability to move after a stroke because nerve cells in the brain die when the oxygen supply is cut off. In a pilot study, Professor Bath's team used a drug to release stem cells from the bone marrow in 36 patients who had recently had a stroke. The method did not cause any harmful side effects. The researchers are now exploring whether these stem cells are able to travel to the brain and whether they can be directed to repair stroke damage when they get there.

Meanwhile, Professor James Fawcett at the University of Cambridge is researching the repair of the central nervous system following injury. In particular, he is studying cells called oligodendrocyte precursor cells. In tissue culture experiments these have the ability to turn back into cells similar to nerve stem cells, and large numbers of them are found at the site of brain injuries. It is possible that these cells can provide stem cells for repairing the brain without the need for transplanting foreign tissue into the body.



Stem cells and the eyes

Stem cells have the potential to restore sight to people with diseases and injuries affecting their eyes. For instance, MRC-funded scientists at the University College London Institute of Ophthalmology are researching stem cell transplants to treat people with hereditary retinal disease and age-related macular degeneration – two major causes of vision problems and blindness in the UK which lack effective treatments. The investigators hope to use stem cells to generate replacement retinal cells that could be used to restore vision. Recently Professor Robin Ali and Dr Robert MacLaren restored sight in mice with photoreceptor loss by transplanting cells called photoreceptor precursors into their retinas. These integrated successfully into the retinas of blind mice and restored some vision. Dr MacLaren said: “This research is the first to show that photoreceptor transplantation is feasible. We are now confident that this is the avenue to pursue to uncover ways of restoring vision to thousands who have lost their sight.”

The cornea is the transparent front layer of the eye that covers the iris and pupil. It is covered by a layer of epithelial cells that are constantly shed and replaced by stem cells from the limbus. But various injuries and illnesses can deplete limbal stem cells. This can cause the epithelial layer to move over the surface of the cornea and results in pain, vision problems and even blindness. Institute of Ophthalmology scientists are also investigating the properties and therapeutic potential of limbal stem cells.

Working collaboratively with colleagues at Moorfields Eye Hospital in London, Institute of Ophthalmology scientists have established the Cells for Sight Tissue Bank – a facility that will help push forward research into corneal stem cell transplants. The bank has Department of Health tissue banking accreditation and holds a Human Tissue Authority licence, which means that stem cells collected and grown there can be used to treat patients.

Rebuilding muscles

Muscle and lean tissue make up about a third of our body. Muscle is vital for movement, metabolic function and maintaining body temperature, and is our chief supply of energy and protein. Decline in muscle size and strength is a major clinical problem in elderly people and many cancer patients. And progressive muscle loss is the cause of disability and eventual death in patients with severe muscular dystrophy. In the future stem cells could be used to rebuild muscle in the elderly or people with injuries or diseases.

Investigators at the MRC Clinical Sciences Centre showed in 2005 that satellite cells – which are responsible for repairing muscle – act like stem cells. They investigated the behaviour of satellite cells by grafting small numbers of them attached to individual muscle fibres into mice with muscle deterioration. They found that each satellite cell produced vast amounts of new muscle and, at the same time, seeded the surrounding region with large numbers of new satellite cells, confirming that they can self-renew like stem cells.

Beneath the skin

Burns victims, elderly people with slow-healing wounds and injury patients often need skin grafts to replace their damaged tissue. Sometimes, an area of skin is taken from an undamaged part of their body and transplanted onto the injured or burnt site. Or large amounts of healthy skin

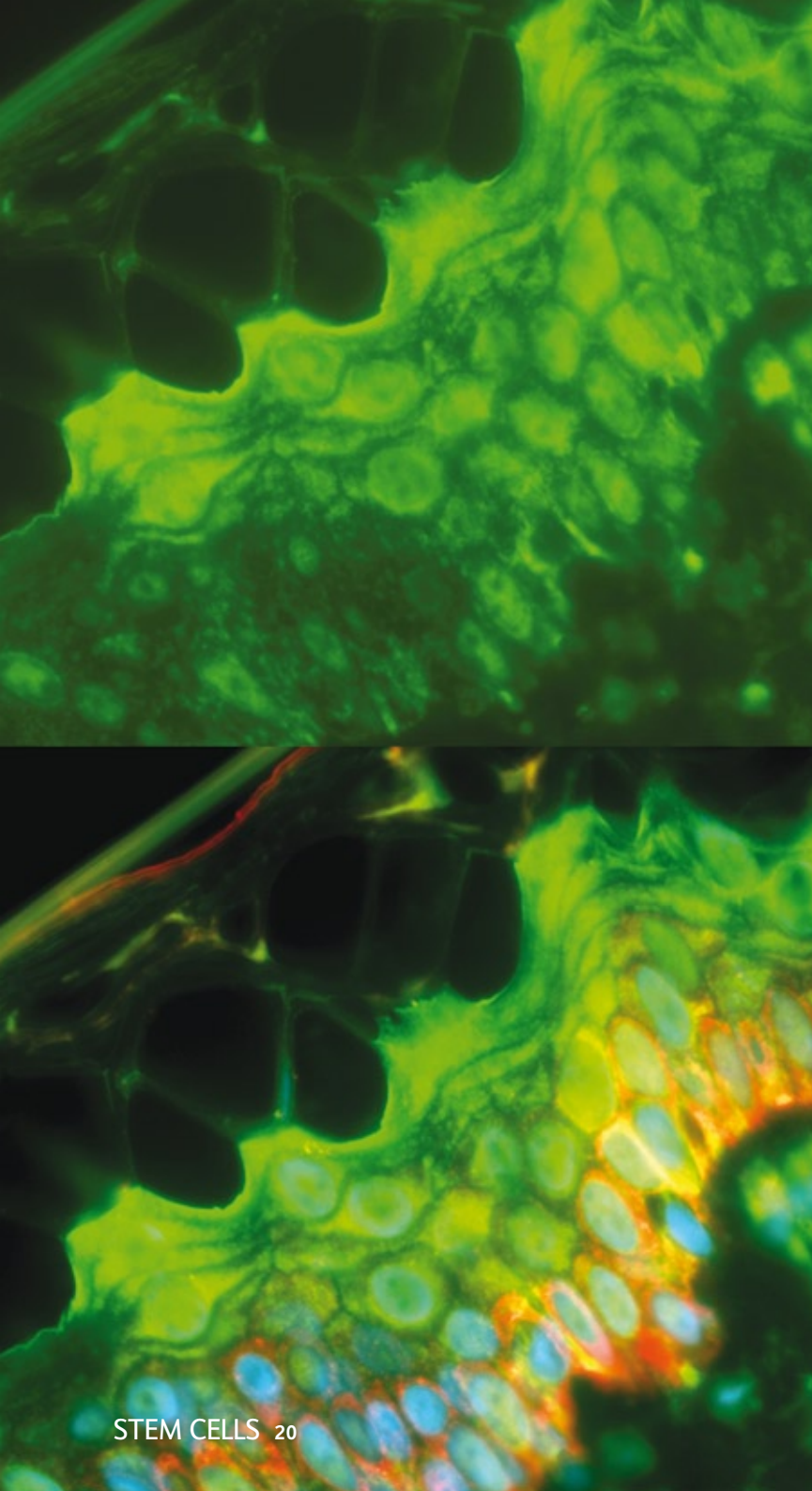
for grafts can be grown in the laboratory – a feat that is made possible by the stem cells that are present in the basal layer of skin. But radical improvements are needed in laboratory-grown skin products before they will be a valuable and cost-effective treatment.

The MRC provides funding to the UK Centre for Tissue Engineering – a collaboration between the Universities of Manchester and Liverpool. Scientists there are investigating new approaches to skin engineering to help with wound healing and burn treatment. Their work spans a wide spectrum – from finding out how to best extract stem cells from the blood and encourage them to develop into skin cells, to identifying the best ways of transplanting artificially-grown skin onto patients.

Strong bones

Stem cell technology also holds promise for many people with bone problems, such as arthritis and osteoporosis patients, people with bone injuries and those who need joint replacement operations.

For nearly a decade, scientists have known broadly the right chemical conditions required to encourage unspecialised stem cells from a patient's bone marrow to change into bone and cartilage cells in the laboratory. Now, scientists at the Scottish Centre for Regenerative Medicine in Edinburgh are using this knowledge to develop a revolutionary way to mend damaged bones and cartilage using a patient's own stem cells. The initiative involves using a 'bioactive scaffold' made to protect the stem cells and stimulate their growth into bone or cartilage once they are placed in an affected area. It could have a major impact on treating conditions such as osteoarthritis, as well as on treating trauma victims whose bones have been shattered beyond repair. Researcher Dr Brendon Noble said: "This is a novel approach in terms of treating damaged bones and cartilage. The aim is to translate the knowledge we've gained from bone biology studies into tangible treatments for patients."



Blocking cancer

An MRC and Leukaemia Research-funded team led by Professor Tariq Enver of the MRC Haematology Unit has for the first time identified pre-leukaemic stem cells, by studying blood from Isabella Murphy, whose identical twin sister Olivia had the disease. Professor Enver explained: "Previously, no-one knew much about the nature or role of stem cells in childhood ALL in either its earliest 'pre-leukaemic' manifestation or in the fully transformed malignant state. Because pre-leukaemia changes in the blood are clinically silent, it was only by finding a twin of someone with the disease that it was possible to identify this early stage of disease before the cells turned cancerous." In samples of Isabella's blood, the researchers were able to identify cells in which abnormal fusion of two genes occurred during the mother's pregnancy, to create a hybrid protein called 'TEL-AML1'. Then, by studying Olivia's blood, they were able to identify the cancer stem cells that the pre-leukaemic stem cells turned into to cause and maintain leukaemia. The finding was confirmed when the scientists put the abnormal gene into human cells which were transplanted into mice with no immune system, which led to pre-leukaemic stem cells becoming established in the bone marrow of the mice. This proved the 'self-renewing' nature of the cells and confirmed a direct link between the genetic malfunction and the generation of pre-leukaemic stem cells. The scientists are now trying to find out what triggers the pre-leukaemic stem cells to turn leukaemic, and to improve understanding of what regulates the cancer stem cells. Professor Enver said: "We hope that eventually our work will lead to therapies to target both the pre-leukaemic stem cell and the cancer stem cell itself, to cure leukaemia while avoiding the debilitating and often harmful side effects of current treatments."

Curing diabetes

There are two main types of diabetes, both caused by problems with regulating the amount of glucose in the blood. Normally the hormone insulin, produced by 'islet' cells in the pancreas, helps to move glucose from the

bloodstream into the rest of the body's cells where it is used as a source of energy. Diabetes develops when the pancreas stops producing insulin (type 1) or when the body does not respond properly to the insulin it produces (type 2). This leads to a build-up of glucose in the blood. Untreated diabetes causes symptoms ranging from fatigue and extreme thirst to coma and even death. According to Diabetes UK, three million people in the UK have diabetes – including up to a million who might not even know.

One of the most promising ways of curing diabetes would be to restore the function of the islet cells. Potentially, stem cells could generate limitless supplies of islet cells for transplanting into patients. Scientists in the Cambridge Stem Cell Initiative are investigating why islet cells are damaged or destroyed in patients with type 1 diabetes, how to stop this happening and how to replace the damaged cells with healthy ones.

Replacing organs

As well as all of the potential uses for stem cells to improve human health outlined above, there are also other possibilities. For instance, in the future, stem cell science might enable scientists to grow replacement tissues and even whole organs for people who need organ transplants. Using a patient's own stem cells would remove the risk of rejection, so they would not need to take immunosuppressant drugs for the rest of their life.

Blood-forming stem cells have already been shown to reconstitute damaged and normal liver tissue. Professor David Adams at the University of Birmingham is trying to find out exactly how these stem cells migrate into liver tissue – research that might lead to new ways of delivering stem cells to the liver to improve the efficiency of stem cell therapy in liver disease.

Testing drugs

Stem cells could also be a valuable aid in drug development. Large numbers of a particular type of cell could be grown for use by researchers when testing new therapies. This would be especially useful for screening potential drugs for toxicity or their impact on a disease and might reduce the need for animal testing. But to be able to do so effectively, scientists will first need to learn how to control stem cell specialisation very precisely.

The MRC is part of the Stem Cells for Safer Medicines Initiative, a public-private partnership involving government, research councils and industry. The initiative aims to facilitate the use of stem cells in early drug discovery by focusing on key scientific challenges and by producing standard protocols. In the long term, the group hopes to develop a bank of human cell lines that can be used to test drugs.





Our UK partners

The MRC is working with several UK partners to help take forward stem cell research. These include the Government-led UK Stem Cell Initiative, the UK Stem Cell Funders Forum (which was set up to take forward the recommendations of the initiative) and charities, including the UK Stem Cell Foundation, which aims to support stem cell research with direct potential clinical benefit to patients.



"I am left in no doubt that if we are to remain world leaders in this crucial area of medical research, then it needs to be given an additional boost in the form of extra financial support and a long-term commitment at the highest level. If this happens, it is probable that a significant proportion of discovery and innovation in the field of stem cell research will take place in the UK."

SIR JOHN PATTISON, CHAIRMAN OF THE UK STEM CELL INITIATIVE

UK Stem Cell Initiative

The UK Government set up the UK Stem Cell Initiative in March 2005, with the aim of working with the public and private sectors to draw up a 10-year vision for UK stem cell research.

Led by Sir John Pattison, the initiative involves representatives from the MRC, the Biotechnology and Biological Sciences Research Council, the Department of Health, the Academy of Medical Sciences, medical research charities, including the UK Stem Cell Foundation, and industry. In late 2005 it reported that the UK is a world leader in stem cell research and development – but that more investment is needed if this position is to be maintained.

The report also contained 11 recommendations for taking forward stem cell research, including a government partnership with industry, creating centres of excellence and improving public dialogue.



UK Stem Cell Funders Forum

The UK Stem Cell Funders Forum was set up in 2006 to take forward the recommendations of the UK Stem Cell Initiative. Its members include the MRC and other research councils, major charities working in stem cell research, UK health departments and the Scottish Executive. The forum allows members to discuss and exchange information on their current stem cell work and funding priorities, to work together to identify barriers to stem cell research and ways to overcome these, and to recognise new areas that could benefit from joint funding.

A further part of the forum's remit is to coordinate a public communication framework for stem cell research. This has been taken on by the Stem Cell Communication Coalition, a group made up of representatives from the forum's member organisations and from the Royal Society, the UK Stem Cell Bank and the Human Tissue Authority. Established in 2002, the coalition has coordinated a number of activities including a public survey of attitudes toward the use of embryos in medical research and a campaign to raise awareness among UK patients of the risks of going abroad for unproven stem cell therapy.

Working with charities and other research councils

The MRC works closely with UK charities and other research councils involved in stem cell research. For instance, in 2003 the MRC launched an annual competition for collaborative career development fellowships in stem cell research. The fellowships provide up to three year's funding to support different areas of stem cell science. This was a joint initiative with the Alzheimer's Society, the Biotechnology and the Biological Sciences Research Council, Diabetes UK, the Engineering and Physical Sciences Research Council, Juvenile Diabetes Research Foundation International and the Parkinson's Disease Society.

We also work with the UK Stem Cell Foundation, which was established in 2005 to support the advance of pioneering stem cell research into medical practice. The foundation raises funds from private donations to directly fund projects where research has indicated potential for direct clinical benefit to patients in the short term. As of early 2008, the MRC had approved five joint awards with the Foundation, addressing bone and cartilage repair, liver regeneration and brain repair.

Safeguarding ethical standards

As medical science progresses, new areas of investigation can raise ethical dilemmas. Any justifiable concerns that the public may have must be balanced with the need for scientists to proceed as efficiently as possible with essential research into life-threatening diseases. The MRC is advised by a committee of experts in this respect. All the scientists we fund must comply with UK legislation and follow MRC and other relevant codes of practice, to ensure that their research is conducted according to high ethical standards. We are the leading national source of guidance and advice in this area and produce a wide range of guidelines on ethics and best practice for medical researchers. In 2003 we produced guidance on ethics for all MRC-funded stem cell researchers.

Concerns about embryos and stem cell research

Some people have concerns about stem cell research and, in particular, the fact that some stem cells are obtained from embryos. In the UK, the Human Embryology and Fertilisation Act allows the use of human embryos that are no more than 14 days old to find treatments for serious diseases and for fertility research.

A MORI poll conducted in early 2003 for the Stem Cell Communication Coalition showed that 70 per cent of the UK public supported the use of human embryos for medical research – both for research into fertility and to find treatments for serious diseases. Results from a 2007 opinion survey carried out by the British Market Research Board showed similar levels of support for embryonic stem cell research.

Approval by the research ethics committee

All medical research in the UK involving patients, human tissue or personal data must be approved by an independent research ethics committee before funding can be granted and the research may begin. Each local health authority has its own committee, which is completely independent of both the scientists and their potential funders. The committees ensure that the research complies with legal and ethical requirements that safeguard the rights, dignity and welfare of all participants.

All research using human embryonic stem cell lines in the UK is also overseen by the independent Steering Committee for the UK Stem Cell Bank and for the Use of Stem Cell Lines. This is a non-statutory body that is tasked with checking that all UK research that uses human embryonic stem cell lines complies with UK regulations and the UK's Code of Practice for the Use of Human Stem Cells. Adherence to the code is a condition of award for any research council grant involving human stem cell research. Any research involving human embryos also requires a license from the Human Fertilisation and Embryology Authority (see page 10).



Your questions answered

What are stem cells?

Stem cells are immature cells that have not yet developed into the specialised cells that make up our organs and tissues. Stem cells are able to form many different types of cell and have the ability to make new copies of themselves almost indefinitely.

How might stem cells help improve human health?

Many diseases are caused by the premature death or malfunction of cells. Scientists believe that stem cell therapy may offer a revolutionary way to treat such illnesses by replacing diseased and damaged body tissues with healthy new cells, or by using them to find new drugs.

What is the difference between embryonic and adult stem cells?

Embryonic stem cells come from embryos that are about five days old. At this stage the cells haven't yet specialised into the different types that make up the human body. Adult stem cells are more specialised, so are more restricted in the type of cell they can form.

How far away are stem cell-based treatments?

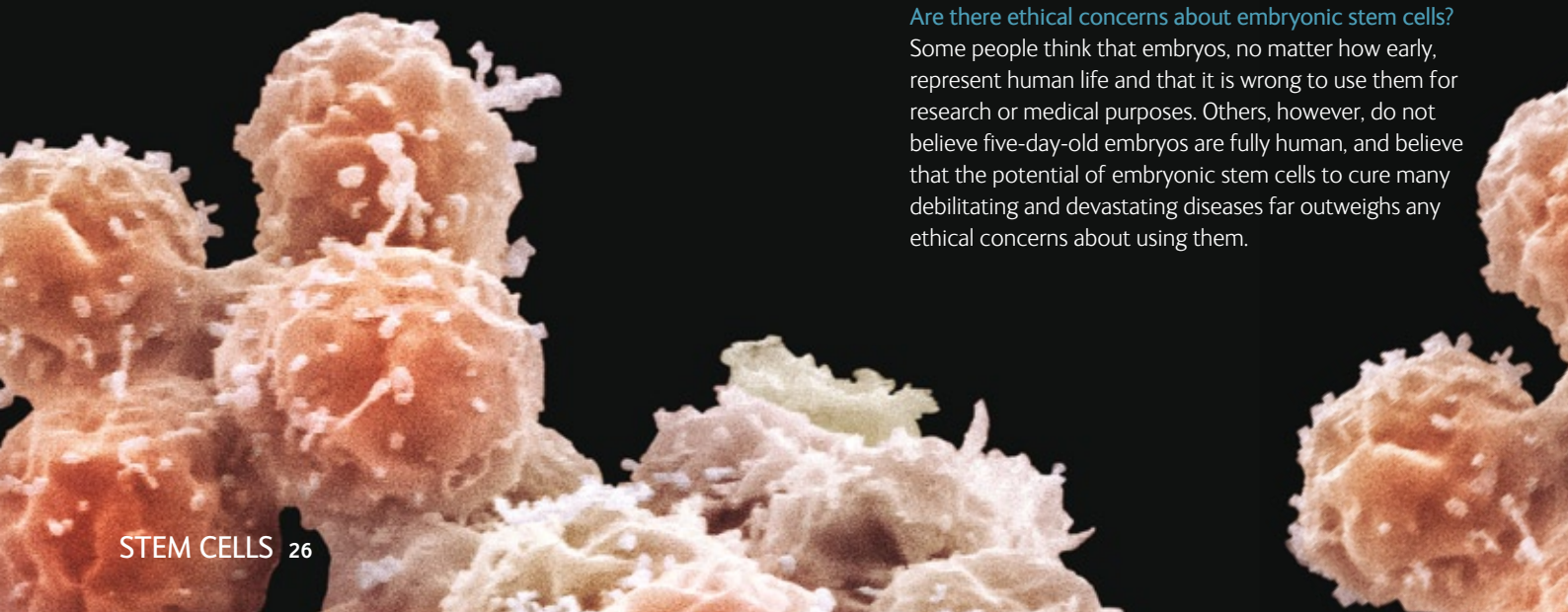
A huge amount of research is still needed before embryonic stem cell therapies will be used to treat patients, although clinical trials testing these may only be a couple of years away. Researchers don't yet understand exactly how stem cells work. In the UK clinicians have been testing the use of adult stem cells to repair blood for some time, for instance in bone marrow transplants, and trials are now underway testing adult stem cells for the repair of other tissues and organs.

How is stem cell research regulated?

In the UK, the Human Fertilisation and Embryology (HFE) Authority regulates all research using human embryos under the 1990 HFE Act. The Act states that embryonic stem cells may only be obtained from donated embryos left over from in vitro fertilisation, or through somatic cell nuclear transfer (see page 5). Embryos may only be used for research until they are 14 days old. The use of human embryonic stem cell lines in the UK must adhere to a code of practice, which is overseen by the UK Steering Committee for the UK Stem Cell Bank and the Use of Human Stem Cell Lines.

Are there ethical concerns about embryonic stem cells?

Some people think that embryos, no matter how early, represent human life and that it is wrong to use them for research or medical purposes. Others, however, do not believe five-day-old embryos are fully human, and believe that the potential of embryonic stem cells to cure many debilitating and devastating diseases far outweighs any ethical concerns about using them.



Working with you

The public plays an essential part in the work of the MRC. Here are some examples of how we are working to communicate the science of stem cells and to find out about any expectations and concerns you might have.

Continuing dialogue

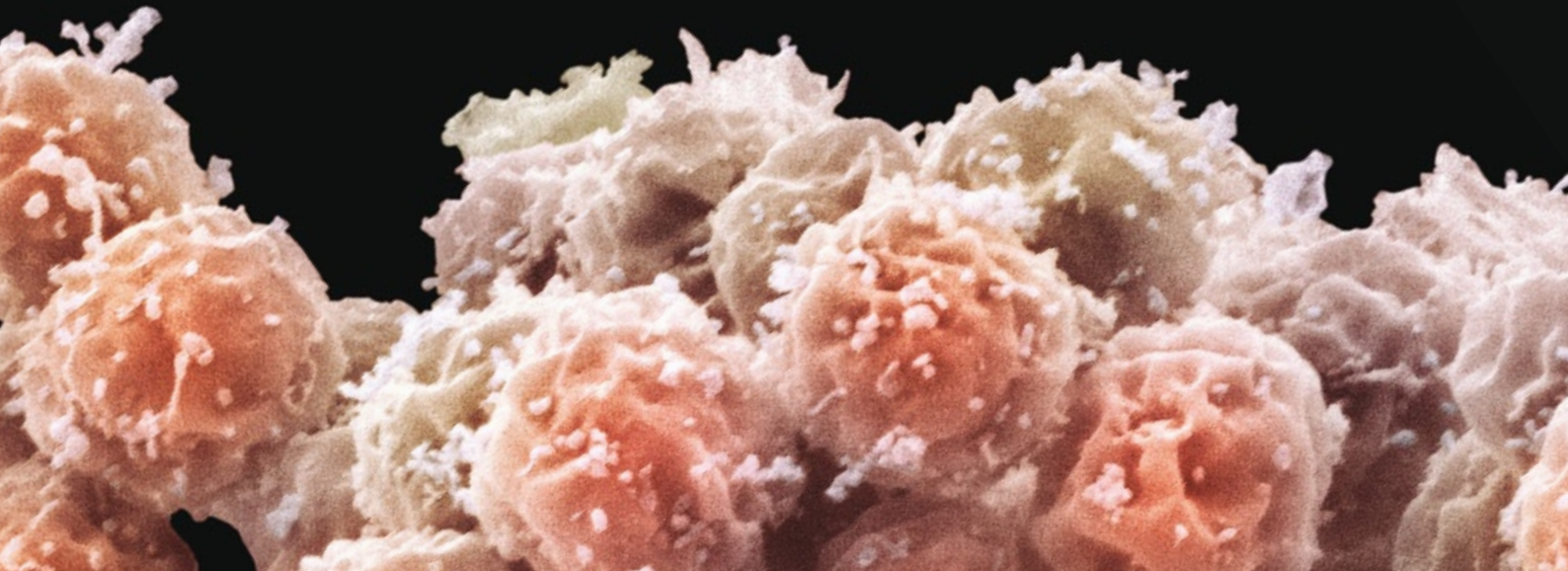
The UK public is generally supportive of stem cell research. However, it is important to us to create opportunities for continuing dialogue, to help us understand people's concerns and expectations and to provide up-to-date information about research developments.

One of the ways we aim to achieve this is with the stem cell exhibition launched in June 2006 by the MRC and the Biotechnology and Biological Sciences Research Council. As this exhibition tours the country, we are holding associated events with stem cell scientists, policymakers and the public. As well as explaining key messages about stem cells and their importance in medical research, the exhibition presents challenges: for the public, on the ethical

and moral acceptability of using stem cells in research; and for policymakers and scientists who must balance public expectation with scientific reality. A range of arguments and points of view are presented and visitors are encouraged to reach their own conclusions about stem cell research.

Working with scientists and the media

It's also important that the science of stem cells is explained in ways that are understandable and assessable to all of us. Therefore, we are working with our scientists to help them develop their skills in speaking about their work. We are also working with the media to help them report on research in a responsible and informed way.



Find out more

If you would like to find out more about MRC-funded research into stem cells, visit our website or the websites of our units, institutes and centres working in stem cell research. Or you can visit any of the other websites on this page to find out more about different perspectives on stem cell science, from charities working in the field to other research councils and regulatory authorities.

Useful web links

- » **Medical Research Council** www.mrc.ac.uk
- » Academy of Medical Sciences www.acmedsci.ac.uk
- » Alzheimer's Society www.alzheimers.org.uk
- » Association of Medical Research Charities www.amrc.org
- » Biotechnology and Biological Sciences Research Council www.bbsrc.ac.uk
- » British Heart Foundation www.bhf.org.uk
- » Cambridge Stem Cell Initiative www.stemcells.cam.ac.uk
- » Cancer Research UK www.cancerresearchuk.org
- » Diabetes UK www.diabetes.org.uk
- » Economic and Social Research Council www.esrc.ac.uk
- » Human Fertilisation and Embryology Authority www.hfea.gov.uk
- » Human Tissue Authority www.hta.gov.uk
- » International Stem Cell Forum www.stemcellforum.org
- » Juvenile Diabetes Research Foundation www.jdrf.org.uk
- » Leukaemia Research www.lrf.org.uk

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- » MRC Clinical Sciences Centre www.csc.mrc.ac.uk
 - » MRC Molecular Haematology Unit www.imm.ox.ac.uk/groups/mrc_molhaem/
 - » MRC National Institute for Medical Research www.nimr.mrc.ac.uk
 - » Parkinson's Disease Society www.parkinsons.org.uk
 - » Scottish Centre for Regenerative Medicine www.scrm.ed.ac.uk
 - » The Royal Society www.royalsoc.org
 - » The Wellcome Trust www.wellcome.ac.uk
 - » UK National Stem Cell Network www.uknscn.org
 - » UK Stem Cell Bank www.ukstemcellbank.org.uk
 - » UK Stem Cell Foundation www.ukscf.org
 - » UK Stem Cell Initiative www.advisorybodies.doh.gov.uk/uksci/
 - » University of Sheffield Centre for Stem Cell Biology <http://cscb.shef.ac.uk>

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