ACADEMY STATEMENT

Stem cell research – progress, hopes and concerns

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Stem cell research — progress, hopes and concerns

Many illnesses, such as diabetes and Parkinson's disease, are characterised by cell loss. Stem cell research has attracted keen interest and raised hopes for new therapies to replace the lost cells.

For the past few decades, two well-established stem cell therapies have been used routinely and saved many lives. One is bone marrow transplantation, where blood-forming stem cells from the bone marrow are transplanted to treat various types of leukaemia, for example. In the other, skin transplantation, new skin is made from the patient's own skin stem cells for the treatment of severe burns. In addition to transplantation, there are pharmacological compounds that promote new cell production by the patient's own stem cells. One such compound is erythropoietin, which stimulates production of red blood cells and offers an alternative to blood transfusion.

Stem cell research has made significant progress to date. But it has also been the subject of much debate, and a great deal of research is still needed to develop novel therapies. A Working Group appointed by the Class for Medical Sciences of the Royal Swedish Academy of Sciences wrote this statement to explain the science behind some much-discussed issues.

The Group identified three particularly important and topical issues:
the need for research on human embryonic stem cells, expectations for the development of new stem cell-based therapies, and 'stem cell tourism'.

The conclusions may be summarised in three points:

- Production of induced pluripotent stem (iPS) cells is a breakthrough in stem cell research that, in the long term, may reduce the need to use human embryonic stem cells. However, at this stage it is very important to conduct research on multiple stem cell types in parallel. Prohibiting research on human embryonic stem cells would be a major mistake.
- Representatives of the scientific community should emphasise both the potential and the complexity of this research. The stem cell field offers numerous new opportunities for drug development and therapy, but giving a time frame in which new treatments may become a reality is often difficult.
- Patient safety always comes first, and development of new therapies must invariably have a sound scientific basis. This must be pointed out in the discussion of stem cells, as well as in other contexts where new research attracts rogue operators.

Dictionary

Stem cells are immature cells capable of giving rise to specialised cells, such as skin or nerve cells.

Embryonic stem cells are derived from the early embryo. They can develop into unlimited numbers of new cells of all the different cell types in the body.

Adult stem cells are present in many organs in the adult body. For any given organ, they can replace lost cells by giving rise to cells of the types present in that organ.

Mesenchymal stem cells are adult stem cells present in the bone marrow that can mature into connective tissue cells, for example.

Induced pluripotent stem cells, iPS cells, are almost identical to embryonic stem cells but derived from reprogrammed mature cells instead of embryos.

Importance of research on human embryonic stem cells

Around the year 2000, the ethics of research on human embryonic stem cells was discussed intensively in many countries. Since stem cells can undergo an infinite number of divisions and have the potential to give rise to every cell type in the body, they are highly valuable in basic research and drug development. They are also a potential source of cells for transplantation. Embryonic stem cells can be isolated from embryos only within a few days after fertilisation. The technique was initially established using mouse cells, an advance of tremendous importance for medical research for which the Nobel Prize in Physiology or Medicine was awarded in 2007. The procedure for culturing stem cells from human embryos, which revolutionised the study of human cells, was first described in 1998.
Embryonic stem cells are isolated from embryos fertilised in vitro that are judged incapable of further development into viable foetuses. In some quarters, studying human embryos is regarded as ethically challenging despite its considerable value for medical research. One argument has been that human embryonic stem cells are not unique and that stem cells present in several adult organs — 'adult stem cells' — can be studied instead. However, it is clear that embryonic and adult stem cells are not identical: only embryonic stem cells continue to divide indefinitely and can give rise to all the tissues in the body. This has prompted acceptance of, and investment in, research on human embryonic stem cells in many countries, including Sweden.

The question of whether human embryonic stem cells need to be studied has been re-examined in the past few years, following unexpected progress in stem cell research. In 2006 a Japanese group headed by Professor Shinya Yamanaka showed that mature, specialised cells could be changed into cells with characteristics very similar to those of embryonic stem cells. Introducing specific genes causes mature somatic cells to lose their specialised abilities and return to a stage almost identical to that of early embryonic cells. This technique, known as 'reprogramming', results in 'induced pluripotent stem cells' (iPS cells). With the rapid growth of interest in and use of iPS cells, reprogramming is now used in research and drug development all over the world. There are considerable expectations that iPS cells will eventually be usable for producing specialised cells suitable for transplantation. Professor Yamanaka was awarded the Nobel Prize in Physiology or Medicine in 2012 for his discovery that adult cells can be reprogrammed to form iPS cells. He shared the prize with Professor Sir John Gurdon, whose groundbreaking frog studies showed that the nucleus of an adult somatic cell retains all the information necessary to make an embryo. Later studies showed that this finding was applicable to mammals as well, and the first specimen — Dolly, the cloned sheep — was presented in 1997.

The ability to reprogramme adult cells to a stage at which they closely resemble embryonic stem cells has raised the question of whether studying iPS cells alone, thereby avoiding the ethically controversial use of human embryonic stem cells, is sufficient. However, although being able to establish and study iPS cells is an enormous advance that has taken place very rapidly, these cells are not, as we have seen, entirely identical to embryonic stem cells.

The Academy therefore considers it essential to study the different types of stem cells in parallel, and most scientists in the stem cell field share this view. Studies on the various types of stem cells will cross-fertilise ideas and techniques. Moreover, we remain unable to judge which cell type will be best suited to potential future medical therapies, since both types (embryonic stem cells and iPS cells) have their advantages and disadvantages. For example, certain protocols used for producing iPS cells may cause cell transformation and tumour growth. Therefore, although

there is considerable hope that this risk can be avoided in the future, more research is clearly needed. Ending research on human embryonic stem cells would be a mistake.

All in all, we find further studies on human embryonic stem cells, in parallel with the study of iPS cells, essential.

Expectations of new stem-cell-based treatments

With mass awareness of stem cell research, which emerged around the turn of the millennium, great expectations arose. Serious illnesses would soon, it was thought, become treatable with new stem-cell-based strategies. The initial excitement has, for some, given way to a certain disappointment that such developments have yet to be realised, despite the initial promise of stem cell research. However, it is important to emphasise that the development of new clinical treatments requires a great deal of time and effort. Developing a new drug typically takes about 20 years, mostly because very thorough and exacting evaluation of safety and efficacy is crucial to the process. This makes it very difficult to predict future scientific breakthroughs and advances that may yield clinical developments. Stem cells are claimed to be potentially useful for treating virtually all human diseases but this, of course, is completely unrealistic.

In the past decade there have been major advances in stem cell research. We now understand the clinical potential of stem cells better. Their limitations for treating certain diseases have also become more evident. For example, in contrast to initial belief, stem cells derived from umbilical cord blood lack pluripotency — that is, the capacity to generate many clinically interesting cell types. Some other areas, such as directed differentiation of stem cells into pancreatic endocrine cells that could potentially be transplanted into patients with Type 1 diabetes, have also proved more challenging than anticipated.

However, other lines of investigation have been remarkably successful. Swedish scientists have, for example, been at the forefront of efforts to create the type of neuron that degenerates in sufferers from Parkinson's disease. Creation of iPS cells (see above) is a major breakthrough in medical research as a whole, and within a few short years this technology has spread to all major research institutes around the world. The ability to generate iPS cells from patients with various disorders has opened up entirely new avenues for studying disease and developing new diagnostics and treatments. A number of new stem cell treatments have already been evaluated in patients. For example, studies in Sweden were the first to show that mesenchymal stem cells transplanted into patients prior to bone marrow transplantation can suppress potentially life-threatening immune rejection. These studies are now being followed up at a number of clinical centres around the world.

The Working Group emphasises the vital efforts being made by the scientific community to explain complex medical research and associated difficulties in rapidly developing new treatments for disease. This is also, of course, relevant to any discussion of the promise of stem cell research.

Stem cell tourism

Besides the stem-cell-based therapies that are now in routine clinical use (bone marrow and skin transplantation), stem cells are now used in certain clinics to 'treat' a wide variety of diseases without scientific documentation of benefits or risks. Patients are invited to travel to countries where this is allowed, giving rise to the term 'stem cell tourism'. It is easy to understand sufferers and their relatives who are tempted by promises of symptom relief or cure of serious or deadly diseases.

The benefits of new medical treatments must be weighed against their risks, and their evaluation must be scientifically based. The common denominator of stem cell treatments offered on a commercial basis for severe illnesses is often the lack of any assessment of either potential benefits or risks to patients. In some cases, independent scientists following up patients subjected to such treatments have found serious adverse events but no benefits. One example is a case of a child who developed a tumour from the transplanted cells.

Development of new medical treatments must always be based on scientific evidence, to ensure that patients are not harmed and to maximise the chances of relieving suffering or curing disease. The Royal Swedish Academy of Sciences supports the Guidelines for the Clinical Translation of Stem Cells developed and adopted by the International Society for Stem Cell Research (ISSCR) in December 2008.

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