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Zellen, die die Politik bewegen

Embryonale und adulte Stammzellen: Chancen und Hürden bei der Entwicklung neuer Therapien

Kurzfassung der TA-SWISS Studie «Menschliche Stammzellen»

Des cellules qui remuent la politique

Élaboration de nouvelles thérapies à base de cellules souches embryonnaires ou adultes: Perspectives – Obstacles

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Embryonic and adult stem cells: opportunities and hurdles, surrounding the development of new treatments

Summary of the TA-SWISS study «Human Stem Cells»

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Dr. Adrian Rüegsegger, Bern, Dr. Bärbel Hüsing, Karlsruhe

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Die Studie wurde von folgenden **Autorinnen** und **Autoren** verfasst:
Auteurs de l'étude:
Authors of the TA study:

Dr. Bärbel Hüsing (Projektleitung)**, Dipl. Sozialwissenschaftler Rainer Frietsch**
Dr. Sibylle Gaisser, Dr. Klaus Menrad, Dr. René Zimmer
Fraunhofer-Institut für Systemtechnik und Innovationsforschung (Fraunhofer ISI)
Breslauer Strasse 48, 76139 Karlsruhe, Deutschland, e-mail: baerbel.huesing@isi.fhg.de

Prof. Dr. Eve-Marie Engels, Dipl.-Biol. Lilian Schubert
Lehrstuhl für Ethik in den Biowissenschaften, Eberhard-Karls-Universität Tübingen
Sigwartstrasse 20, 72076 Tübingen, Deutschland
e-mail: eve-marie.engels@uni-tuebingen.de

Dr. Beatrix Rubin
Institut für Angewandte Ethik und Medizintechnik, Medizinische Fakultät, Universität Basel, Missionsstrasse 21, 4055 Basel, Schweiz, e-mail: Beatrix.Rubin@unibas.ch

Prof. Dr. Rainer Schweizer
Forschungsgemeinschaft für Rechtswissenschaft, Universität St. Gallen,
Tigerbergstrasse 21, 9000 St. Gallen, Schweiz, e-mail: rainer.schweizer@unisg.ch

Betreuung der TA-SWISS Studie – Responsable de l'étude – Supervisor ot the TA-SWISS study
Dr. Adrian Rüegsegger, Zentrum für Techologiefolgen-Aschätzung, Bern

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Zentrum für Technologiefolgen-Abschätzung
Birkenweg 61, CH-3003 Bern
Tel. (+41) 031 322 99 63, Fax (+41) 031 323 36 59
E-Mail ta@swtr.admin.ch
Internet www.ta-swiss.ch – www.publiforum.ch

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The Centre for Technology Assessment is attached to the Swiss Science and Technology Council, which advises the Federal Council on scientific and technological issues.

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Die Studien des Zentrums für Technologiefolgen-Abschätzung TA-SWISS sollen möglichst sachliche, unabhängige und breit abgestützte Informationen zu den Chancen und Risiken neuer Technologien vermitteln. Deshalb werden sie in Absprache mit themenspezifisch zusammengesetzten Expertengruppen erarbeitet. Durch die Fachkompetenz ihrer Mitglieder decken diese so genannten **Begleitgruppen** eine breite Palette von Aspekten der untersuchten Thematik ab.

Le Centre d'évaluation des choix technologiques TA-SWISS se doit, dans toutes ses études sur les avantages et les risques potentiels des nouvelles technologies, de fournier des informations aussi factuelles, indépendantes et étayées que possible. Il y parvient en mettant chaque fois sur pied **un groupe d'accompagnement** composé d'experts choisis de manière à ce que leurs compétences respectives couvrent ensemble la plupart des aspects du sujet à traiter.

Studies carried out by the Centre for Technology Assessment TA-SWISS are aimed at providing information concerning the advantages and risks of new types of technology which is as factual, independent and broad as possible. For this reason they are conducted in collaboration with groups of experts in the corresponding field(s). Thanks to the expertise of their members, these so-called **supervisory groups** cover a broad range of aspects of the issue in question.

Folgende Personen wirkten bei der TA-SWISS Studie «Menschliche Stammzellen» in der **Begleitgruppe** mit:
Le groupe d'accompagnement de l'étude «Cellules souches humaines» se composait des personnes suivantes:
The following people were members of the **supervisory group** for the «Human Stem Cell» study:

Sibylle Ackermann	Institut d'Ethique et des droits de l'homme, Université Fribourg, Fribourg
Prof. Kurt Bürki	Institut für Laborkunde, Universität Zürich, Zürich
Dr. Reto Guetg	Konkordat der Schweizerischen Krankenversicherer, Solothurn
Dr. Uwe Junker	Novartis Pharma AG, Basel
Dr. Margrit Leuthold	Schweizerische Akademie der Medizinischen Wissenschaften, Basel
Prof. Alex Mauron	Bioéthique/CMU, Université de Genève, Genève
Prof. Catherine Nissen-Druey	Departement Forschung, Kantonsspital Basel, Basel
Prof. Hans-Peter Schreiber	Ethik-Stelle, ETH Zentrum, Zürich
Dr. Verena Schwander	Bundesamt für Gesundheit, Bern
Verena Soldati	Basler Appell gegen Gentechnologie, Basel

Cells that are causing a political stir

Embryonic and adult stem cells: opportunities and hurdles, surrounding the development of new treatments

Summary of the TA-SWISS study «Human Stem Cells»

Contents:

Top-level debate

There have been few developments in biomedicine that have triggered such passionate debates in numerous countries within just a few years as research on human embryonic stem cells. While researchers are holding out the prospect of new forms of treatment for hitherto incurable diseases, critics are emphasising the inviolability of the human embryo that is the source of these cells. Politicians are being called on to establish a legal framework that as well as the needs of sick people and the freedom to carry on research, also takes into account ethically tenable treatment of unborn life.

On 22 April 2001 a letter arrived at the White House, bearing the signatures of 80 Nobel prize winners. These eminent scientists were writing to President George W. Bush, voicing their concerns and asking him to make government funds available for research into human embryonic stem cells. The President had previously refused to support this branch of research with public money because the harvesting of such cells from embryos just a few days old raised all kinds of ethical questions. «Pro life» groups, the active anti-abortion lobby in the US, had already protested against proposals to subsidise this research with taxpayers' money.

Research on embryonic stem cells of mice has been going on for some twenty years. But it was only in 1998 that a team of researchers in the US succeeded in reproducing corresponding human cells in the laboratory. As a result huge expectations were raised for new treatments for previously incurable diseases, because embryonic stem cells have the potential to develop into all types of body cells and tissues. Teams of researchers all over the world would now be looking to explore the possibilities of these cells, and ideally to convert these possibilities into practical applications. And not least, there are also major economic interests behind the stem cell research. It is therefore no surprise that the aforementioned campaign was organised by two researchers from Advanced Cell Technology, a company that carries out research into stem cells and cloning methods.

In August 2001 the President turned his attention to stem cell research: in a detailed statement, President Bush discussed his decision to make government funding available

only for research on the 60 or so types of cell cultures (known as cell lines) that private companies had already harvested from embryos prior to 9 August 2001. «The life and death decision» had already been made for these embryos, said Bush, and it would not be crossing a fundamental moral line if we were to do it «by providing taxpayer funding that would sanction or encourage further destruction of human embryos».

In Germany, too, the debate about stem cell research permeated the very highest political levels. The background to this was a research application that had been pending for some time at the German Research Council (Deutsche Forschungsgemeinschaft, DFG). The applicants, from Bonn, were trying to win support for a project, in which they were looking to clarify whether nerve cells could be grown from human embryonic stem cells, nerve cells that might, one day, be used to treat nervous disorders. The German law on embryo research, however, prohibits research on embryos if they would be destroyed in the process. That also applied if they were just a few days old, as is the case with stem cell harvesting. So in Germany, the argument flared over the question of whether the sought-after cells could be obtained from other countries, and whether research on imported cells would be permissible. In May 2001, the DFG issued a statement approving these options that were not covered by the law, sparking an intense debate. Prominent figures from the fields of medicine, ethics and the law tried to outdo each other with profound analyses, German Chancellor Gerhard Schröder set up a National Ethics Council, and politicians took up their positions with a view to debating the issue in Parliament. In January 2002 the German lower house, the Bundestag, although it prohibited the import of human embryonic stem cells, at the same time set about formulating a law which would establish exceptions. This «stem cell law» was hurriedly drawn up, and has been in force since 1 July 2002.

In Switzerland, too, it was research that set the pace. In September 2001 the Swiss National Science Foundation (SNF) approved funding for a project by a Geneva-based research group, the aim of which was to grow cardiac muscle cells from imported human embryonic stem cells. These could possibly play some future role in the treatment of heart diseases. Sensitised by developments in other countries and by the attempts of individual members of the Parliament, the Swiss government also decided to regulate the open issues immediately, to ensure that such research projects would not end up in some sort of «legal grey area». The Swiss Federal Council, the Bundesrat, asked the Swiss Federal Office of Public Health (Bundesamt für Gesundheit, BAG) to draw up a separate bill on embryo research, without waiting for the conclusion of the comprehensive legislation on human research. The first draft of the new «embryo research law» was sent in May 2002 for consultation to interested and affected groups. In November 2002, the Bundesrat approved the revised bill and passed it on to the Parliament. The «Science et Cité» Foundation, on the instructions of the Bundesrat, prompted the public debate on stem cell research by holding numerous events during 2002 (see box «Public debate»).

Public debate in Switzerland

By contrast with both Germany and the US, public debate on stem cell research in Switzerland was a fairly quiet affair. Despite extensive activities by the «Science et Cité» Foundation and others at national and local level on this issue, the debate remains largely restricted to specialist groups. One possible reason for this might be the pragmatic approach of the Swiss people to the issues involved. At least, the results of six «publicfocus» events point to this conclusion, events at which the Centre for Technology Assessment, TA-SWISS, held discussion rounds to gauge the opinion of citizens.

Embryo at the 16-cell stage (detail) (pd)

Cells that raise hopes of a cure

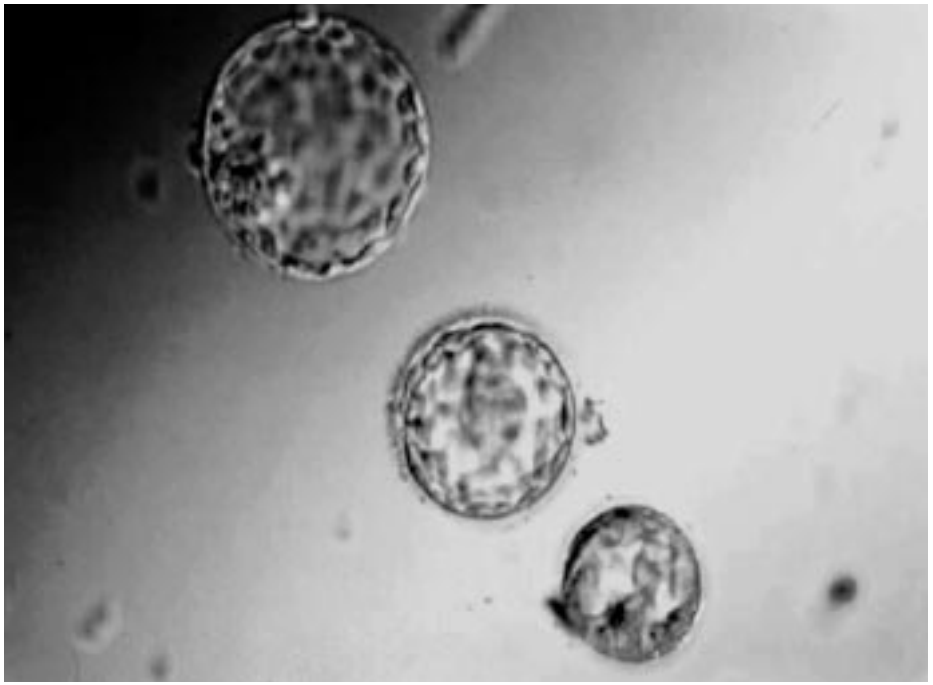
The fascination that surrounds stem cells and the expectations of future treatments is based on the fact that these cells produce all of the two hundred or so different cell types that occur in the human body. Stem cells differ from «ordinary» specialised cells, each of which has quite specific functions, because of two important characteristics: embryonic and adult stem cells can reproduce over a long period by repeated cell division, and this gives them the ability to develop into one or more cell types.

Embryonic stem cells ensure that during the development of the embryo the different cell and tissue types develop first of all. So-called adult or tissue-specific stem cells, which also occur in the adult body, are responsible for the regeneration of tissues and organs. This means that damaged or dead cells are replaced, so that our organs can continue to perform their functions over decades. It is these special characteristics that make stem cells so interesting for medical technical applications. Because of their ability to renew themselves continuously, these cells can be kept in the laboratory, under ideal conditions, for a relatively long time in cell cultures, and also reproduce, which means that new ones do not have to be constantly harvested. Once more is known about the factors that are responsible for the «differentiation», i.e. the specialisation of cells for specific functions, the aim is to use stem cells selectively, to grow them, for example, into cardiac, nerve, skin or muscle cells.

Four new treatment concepts

Through new concepts, it might be possible with human stem cells to realise first-time or improved treatments for serious disorders such as Parkinson's disease, which today cannot be treated, or only inadequately treated. The first concept is based on the reproduction of human stem cells in the laboratory and redeveloping them selectively for suitable cell grafts, to be transplanted into the body of the sick person, where they take over the functions of cells and tissues that are no longer working properly. In the second approach, human stem cells would be transplanted into the patient. The differentiation of the required cells takes place only in the body of the person being treated, controlled by signals from the tissue into which the cells have been transplanted. Under the third concept, the stem cells would be used to grow tissues, which could then be transplanted («tissue engineering»). The fourth approach allows for new types of drug based on discoveries about the reproduction and differentiation of stem cells. These drugs would work on the patient's own tissue-specific stem cells in such a way that impaired cell and tissue functions in the patient's body would be regenerated. The first three treatment concepts referred to above appear essentially to be applicable to both embryonic and adult stem cells; the fourth makes use exclusively of adult stem cells.

If these concepts were one day to be realised, there would exist a huge potential for treatments based on stem cells. In the case of diabetes (diabetes mellitus), for example, people with the disease are able to live a longer, virtually normal, healthy life thanks to a carefully controlled, regular administration of insulin. Nevertheless, it is often impossible to prevent long-term damage such as problems with blood supply to the limbs, kidney failure or even blindness. Cell replacement treatments could help to reduce such long-term damage, as it is hoped that transplanted insulin-producing cells will regulate the concentration of blood sugar in a way that is better tolerated by the body in the long term than is possible with daily insulin injections. Several neuro-degenerative ailments, such as Parkinson's disease, Huntington's disease or multiple sclerosis are caused by certain types of cell in the nervous system no longer functioning properly. If it were possible to grow from stem cells those cells that have been degenerated in the aforementioned diseases, new treatments might possibly be developed. Another area of application could be heart disease. Within certain limits, rehabilitation is possible for people affected by minor damage to the cardiac muscle caused by a myocardial infarction. However, more seriously damaged areas of the cardiac muscle cannot be restored, and transplantation of a healthy donor heart is a difficult and demanding operation – and because of the shortage of donor organs something that can rarely be contemplated. That is why treatments in which the cardiac muscle can be regenerated would be desirable, for example involving the harvesting of cardiac muscle cells from



Embryo at the blastocyst stage, 5 and 6 days after fertilisation (Alan Trounson, Clayton Victoria, Australia)

stem cells and transferring these by injection into the weakened area of the muscle.

Already proven in practice: adult stem cells

Up to now, there have been established cell treatments only in a few areas, such as blood cancer or skin burns, and these use adult stem cells. The best known adult stem cells are those of the blood-forming system, the so-called haematopoietic stem cells. These are also the stem cells that are most commonly used for treatments. Since the end of the 1960s, they have been used to cure serious blood diseases or for the regeneration of the immune system, which is often damaged in cancer treatments by radiation or chemicals. Adult stem cells are found only in very small numbers in the blood or in various tissues (e.g. in the liver, brain and skin), which means that they first have to be enriched if they are to be used for treatments. In this case, the best established are procedures to harvest haematopoietic stem cells from blood or from bone marrow. Another source of such stem cells is blood from the umbilical cord of newborn babies. Because of the small volume of blood in the umbilical cord, however, it is only possible to harvest a small quantity of these neonatal stem cells. Accordingly, it has so far only been possible to treat children who weigh less than 40 kilograms. Provided the parents of the newborn baby agree, umbilical cord blood is stored in public or even commercially-run blood banks. If the child suffers from a serious disease which could be treated with the help of these neonatal stem cells, it will be possible to resort to the stem cells from umbilical cord blood stored in the blood banks.

Adult stem cells offer the advantage that in many cases they may be taken from the same person that they are used to treat. As a result, rejection by the immune system, which is otherwise the biggest problem with the transplantation of cells, tissue and organs, is avoided. However, adult stem cells have not yet been found in all tissues. And, because their functions are limited, it is assumed that they do not offer the same development possibilities as embryonic stem cells. New research findings, however, lead us to suspect that adult stem cells are more versatile than had been thought until recently. If it is confirmed that they can indeed acquire characteristics that are not limited to their tissue-specific function, this could in the future considerably expand their field of application.

The beacon of hope that everyone is waiting for: embryonic stem cells

Public debate about embryo research is focussed on embryonic stem cells. Not until 1998 did a team of American researchers show that it is also possible to cultivate human embryonic stem cells in the test tube. This gave biomedical research a long-awaited breakthrough, as we have been aware for some time of the enormous potential of these cells from the natural development of the embryo. But this potential can only be exploited if they can be grown in cell cultures.

In most cases, human embryonic stem cells are harvested from embryos only a few days old that have been created for the purpose of in-vitro fertilisation (see box «Test tube fertilisation»), but which ultimately are no longer used for this procedure. Such embryos are referred to as «superfluous» or «orphaned» embryos. There are thousands of them stored in hospital deep-freezes all over the world, and they are normally destroyed after being stored for a few years.

Procedure for harvesting embryonic stem cells

Five to six days after fertilisation, the embryo is a hollow, spherically-shaped structure about one-fifth of a millimetre in diameter, known as the blastocyst. The prized cells are taken from its internal cell layer. They can develop into any human body tissue, and are therefore described as pluripotent (see box «What cells can do»). Unlike fertilised egg cells and those cells that are produced in the first three cell divisions, they are no longer totipotent, i.e. it is no longer possible to grow them into a whole organism.

When the stem cells are harvested, the embryo is destroyed, which also gives rise to ethical reservations. Instead of superfluous embryos, it might also be possible to harvest stem cells from embryos specifically created by artificial fertilisation for research purposes. However, the «manufacture» of embryos for research is largely rejected on ethical grounds, and the procedure is therefore banned in many countries, including Switzerland.

«At its core, this issue forces us to confront fundamental questions about the beginnings of life and the ends of science.» George W. Bush

Totipotency, pluripotency and multipotency: what cells can do

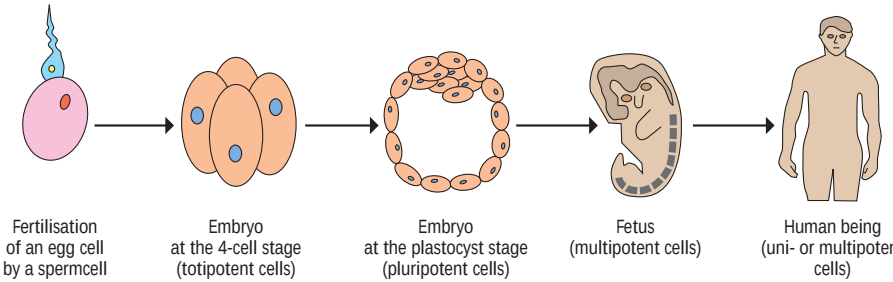
In mammals, the fertilised egg cells and individual cells of the early embryo until it reaches the eight-cell stage have the ability to develop into a complete and viable individual. These cells are described as totipotent, i.e. «capable of everything». Cells at a later stage of embryo development can still produce all types of organism cells and tissues, but are no longer able to develop into a complete individual. Such cells are known as pluripotent, i.e. «capable of much». It is highly likely that these findings from animal experiments could also be applied to humans, but for ethical reasons experiments of this kind are not carried out on humans. The distinction between totipotency and pluripotency is important, as from an ethical and legal point of view it is material whether a cell is able to produce a whole organism or not. In some countries, totipotent cells are subject to the same strict protective regulations as embryos, i.e. they are not available for research, or only in certain exceptional cases. However, research on embryonic stem cells manages without totipotency, as the aim is to produce only cell material, and not whole living beings. Accordingly, interest is centred on pluripotent embryonic stem cells. It is mostly this type of cell that people are referring to when they talk about embryonic stem cells without further precision. They can be harvested from human embryos that are five to six days old. During natural embryo development, cells specialise increasingly in the functions that they assume in the formation of organs or tissues: then they are only able to create a limited number of cell types (multipotency) or even just one specific cell type (unipotency). Those stem cells that are still found in the human body after birth, the so-called adult or tissue-specific stem cells, are uni- or multipotent, which limits the range of applications for future treatments. More recent research findings, however, are suggesting that certain types of adult stem cells could actually be pluripotent, as embryonic stem cells are, and may therefore have greater development potential than previously assumed.

What is known as «therapeutic cloning» is another possibility that some people would like to explore in the future to harvest human embryonic stem cells. This procedure involves the cell nucleus of a body cell (i.e. of a somatic cell) being transferred into an egg cell, whose cell nucleus has been removed beforehand. This technique is therefore also called somatic cell nuclear transfer. Unlike natural fertilisation, where the maternal chromosomes of the egg cell are combined with the paternal genome from the sperm cell, here the egg cell is only «implanted» with the genome of the donor of the cell nucleus. The advantage of this would be that the stem cells grown from these would be genetically identical with the cells of the person from whom the cell nucleus comes. If they could be used to treat that person, they would not be rejected.

The cloning method is being tested on a number of animal species. Using the procedure outlined above, there has already been some success in developing embryos, and in a few rare cases there have actually been some viable animal births, after the clone embryos had been transferred into the uterus of a mother animal. The most famous example of this is Dolly the sheep, which hit the headlines in 1997. In therapeutic cloning, however, there is no cloned offspring. Instead, the embryo would be used to harvest stem cells at the blastocyst stage, just as it is with «superfluous» embryos from in-vitro fertilisation. The entire procedure would therefore take place in the test tube. This procedure has not yet been successful on human cells; in the only known experiment to date, the embryo failed to develop into a blastocyst. However, it is known from animal experiments that the success rate with cloning is very small: firstly, a large number of egg cells are required even to obtain just a few clone embryos. Secondly, most of the embryos «produced» using this technique are seriously damaged. This is because in the «reprogramming» of the transferred cell nucleus a defective activation model (so-called «imprinting») of the gene is released. It is in any case uncertain whether such cells can be used for treatment purposes. Furthermore, from an ethical standpoint cloning technology is controversial. In Switzerland the procedure may not be used on human cells.

This means that not all of the actual or desirable possibilities for obtaining embryonic stem cells have yet been explored. Another procedure uses so-called primordial germ cells as a «source». Such cells are found in the five- to ten-week-old human embryo or foetus. They are also often rather imprecisely referred to as embryonic germ cells (EG cells), because they subsequently develop into sperm or egg cells in the growing individual. The starting material for harvesting these cells are aborted embryos or foetuses, or early spontaneous abortions. Even this method of harvesting embryonic stem cells from humans was only achieved in 1998. Depending on their origin, the corresponding stem cells are also referred to as EG cells. This means that they can be clearly differentiated conceptually from stem cells harvested from blastocysts, which are commonly referred to and which are known by the abbreviation ES cells. According to what is known at present, EG cells are less promising in terms of success than ES cells. This is because they are unable to divide for as long in cell culture, and so it has not previously been possible to grow them in the absence of other cells. Animal ex-

From a fertilised egg cell to a human being



periments also suggest that EG cells do not have the same multiple possibilities to produce different cell types as ES cells. Of greater weight, however, is the observation that these cells show a defective imprinting, which could possibly render them unusable for therapeutic applications.

EG cells, however, would have the advantage that it would not be necessary to destroy potentially viable embryos in harvesting them. But there are also ethical objections to the use of embryonic or foetal tissue from abortions, so the search for further possibilities for obtaining embryonic stem cells will continue. One of these research approaches is seeking to use the principle of parthenogenesis (asexual reproduction). Here, unfertilised egg cells are developed into complete individuals, as is the case, for example, with honey bees and ants. In these insect species the males are produced from the unfertilised egg cells. Parthenogenesis can also occur in mammals, where the chromosome set of the egg cell is duplicated without fertilisation having taken place. However, «embryos» created in this way die at a very early stage. For the harvesting of egg cells, however, it is sufficient for development to reach blastocyst stage. Experiments have now also demonstrated that this is possible in mice and monkeys. Corresponding trials using human egg cells have nevertheless been unsuccessful because the dividing egg cells have failed to develop into blastocysts.

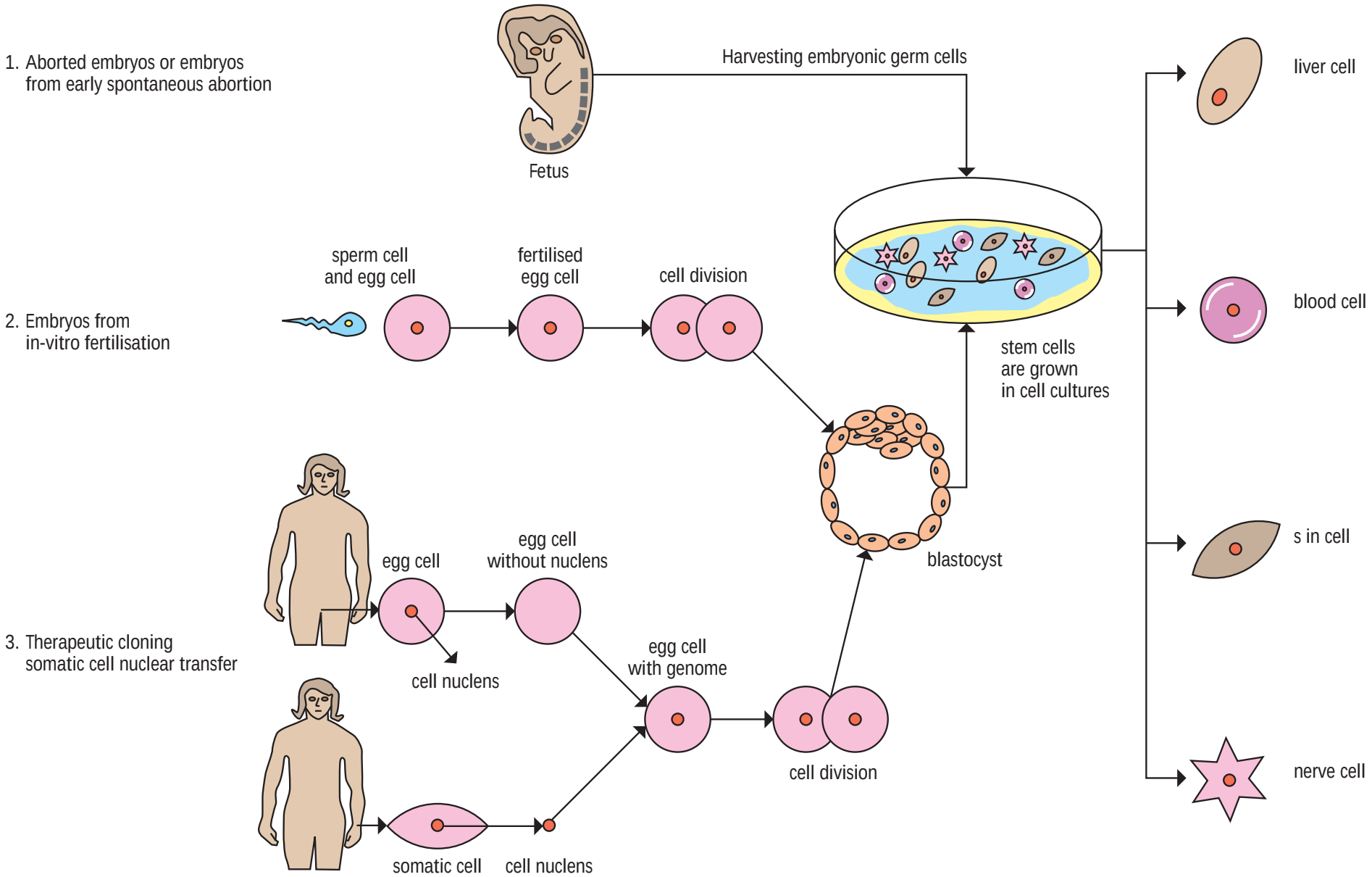
Scientific and technical obstacles holding up treatments

Conceptually, the idea of using human cells to treat diseases is an attractive one. What could be more natural than replacing non-functioning cells with other cells that can carry out their functions in the body? The applications of adult stem cells already in existence have shown that this procedure functions, in principle. Whether the therapeutic possibilities can be expanded is, in the case of adult stem cells, mainly dependent on the extent to which more efficient methods of enriching these cells can be developed, and of increasing their ability to reproduce in cell cultures. Only then can sufficient cell material be made available for treatments. It also remains to be clarified whether adult stem cells could even be pluripotent. If this characteristic were present, or could be selectively brought about, these adult stem cells would possibly be equivalent to embryonic stem cells in respect of their development potential. Furthermore, they have the added advantage that harvesting them is much less problematic, ethically and legally, than the harvesting of embryonic stem cells.

Until embryonic stem cells also provide benefits for sick people, there are still many questions to be resolved. It is still not possible to harvest therapeutically useful cell preparations, and to grow the desired cell types in pure form, either from human embryonic stem cells or from embryonic stem cells of mice – which we have been able to cultivate for over 20 years. This is, however, an essential precondition for being able to use such cells for therapeutic purposes. Moreover, the possibility of embryonic stem cells, or transplants taken from them after transfer into the person being treated, going out of control cannot at present be ruled out. They could form tumours, or develop at the wrong place into the wrong type of cell. Examples of this are known from animal experiments. Also, the risk of infection must be avoided, as until now embryonic stem cells have normally been cultivated in culture media which contain animal cells (known as «feeder layers»). Only recently has there been any success in growing human embryonic stem cells without the addition of animal cells. This means that all cell cultures previously developed could still be «contaminated» with pathogens from animal cells, and therefore of questionable value in treatments. Further unresolved aspects with future cell treatments are technical realisation, the selection of the suitable place in the body for implanting the cell into, and the extent of specialisation and the number of transplanted cells. And not least, a solution must also be found to the problem of rejection of the «foreign» cell by the immune system. Unlike adult stem cells, embryonic stem cells are at present only opening the way for so-called allogeneic cell transplantation, i.e. the cells are not genetically identical with the sick person. Treated persons would therefore have to take drugs to prevent their bodies rejecting the cells, as is the case, for example, with organ transplantation. Only if the concept of so-called therapeutic cloning of human cells were allowed to become reality would it be possible for «patient-compatible» preparations to be created from embryonic stem cells.

Just how much time it will take to develop treatments from human embryonic stem cells is very difficult to estimate, in view of the issues that are still open. Optimistic forecasts suggest that the first applications could be available in as little as five years. Pessimists, however, doubt that treatments based on embryonic stem cells will ever become reality. One estimate frequently quoted by experts considers suitably practical procedures a possibility within the next ten to twenty years. Unfortunately, it is also true that for those diseases that are often referred to as models for cell treatments, such as diabetes and Parkinson's disease, the therapeutic application of embryonic stem cells is currently still hypothetical.

Three possibilities for obtaining embryonic stem cells



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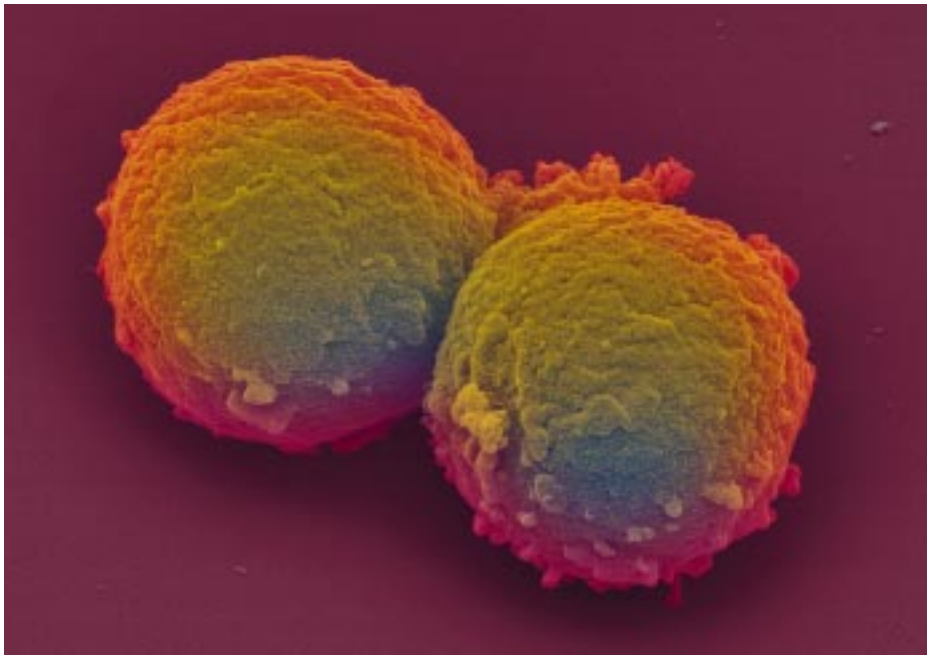
«The State is the only authority that can decide what should or can happen to these embryos.»
Ruth Dreifuss

Dealing with embryos: burning ethical questions

From an ethical point of view, the goal of stem cell research, to help and to heal, is not just a tenable one, but also a desirable one. But even considering these lofty objectives, an embryo is a very valuable commodity, and there is a great deal at stake. It is more than a question of a potentially beneficial «exploitation» of human life at its very earliest stage of development that is doomed to die anyway.

The question of whether embryos may be «consumed» for research and treatment purposes has only arisen since the technology of reproductive medicine made it possible to fertilise egg cells outside the human body (see box «In-vitro fertilisation»). This is because there is of course no question of carrying out research on embryos that develop in the natural environment of the mother's body. Accordingly, it is only so-called «extra-corporeal» embryos that are discussed below, that is, embryos that are created by in-vitro fertilisation or may in future also be created by cell nuclear transfer. It is impossible for such embryos to develop into a child, unless they are implanted into a woman's uterus. But with these embryos, too, the question arises of whether they should be used for research at all, and if so, under what conditions.



Multipotent stem cells from umbilical cord blood (keystone)

«Superfluous» embryos

Embryos just a few days old are also potential living beings, even if they are stored deep frozen in reproductive medicine clinics. They have been created with the intention of fulfilling dreams of having children by couples who are unable to conceive naturally. Occasionally such embryos become «superfluous». Is it ethically acceptable to use these embryos, contrary to their original purpose, for the harvesting of stem cells, even if doing so means «consuming» them?

A highly diverse picture of the moral status of such embryos is emerging from the now barely manageable flood of publications.

- The view that gives the embryo the least protection is based on the assumption that it is no more than a pile of cells. In moral terms, there is no difference between the embryo and any other organ and tissue cells, because outwardly the early embryo is an accumulation of cells, or a spherically shaped object (at the blastocyst stage) and bears absolutely no resemblance to a human being. This view is also known as «reductionism». It conflicts with most people's emotional evaluation and ethical principles.
- The embryo has a higher moral status if it is assumed that its inviolability and right to life grow gradually. In taking this view we are already according the early embryo at least a type of respect. The fertilised egg cell

has only a small right to life, but its inviolability increases as it develops and, in the case of pregnancy, until birth; the infant has a full right to life. For those people who support more extensive protection, this view of degrees of inviolability of life therefore gives rise to criticism largely because they take the view that classifying the right to protection according to specific stages of development is purely arbitrary.

- The strongest implications for dealing with embryos are based on the view that the embryo has the full sanctity of human dignity from the very beginning of its development, and therefore the same unrestricted sanctity of life as a living human being. This view can be further subdivided, depending on which exceptional situations are permitted, such as an aborted pregnancy, in order to deviate from the unrestricted protection of life. The most restrictive interpretation permits no exceptions at all. Less strict variants of this viewpoint permit abortions under more or less restricting conditions.

Advocates of reductionism should have no objection from an ethical point of view if superfluous embryos are used for the harvesting of stem cells. Although supporters of degrees of life protection do not tolerate arbitrary treatment of the early embryo, under this view the harvesting of stem cells is acceptable if certain conditions are met. Among the possible criteria: research on these cells would have to have a realistic connection with future treatments; there is no way of conducting corresponding experiments on other types of cells; and the proposed experiments would have to stand up under strict biomedical and ethical evaluation. For those people who grant the full sanctity of human dignity to the embryo, depending on how strong their views are, there could be no question of conducting research that «consumes» embryos, or only in extremely rare exceptional cases.

«Therapeutic cloning»: a solution not without problems

With so-called therapeutic cloning, using the cell nucleus transfer method described above an embryo would be specifically created to harvest stem cells. Advocates of this procedure emphasise that it does not «misuse» any nascent life, because in this context there is in any case no intention of bringing about a pregnancy, which contrasts with the use of superfluous embryos from in-vitro fertilisation. However, if a cloned embryo is able to develop into a blastocyst, as is necessary for the harvesting of stem cells, the possibility that it would grow into a child if it were transferred into a woman's uterus cannot be ruled out. This type of reproductive cloning works with mammals, as we have seen with Dolly the sheep. Reproductive cloning is rejected in principle by serious researchers, but there are individuals who are prepared to take the risk and put this procedure into practice. This raises some urgent ethical questions: if a cloned embryo can, in principle, develop into a human being, is it then less deserving of protection than one that has been created by the fertilisation of an egg cell by a sperm cell? Is it permissible to push ahead with the technique of therapeutic cloning if it is based on the same principle as the frowned-upon technique of reproductive cloning? The high demand for human egg cells is another argument against therapeutic cloning. This is because the procedure, which is in any case an inefficient one, would have to be carried out very often to obtain a sufficient quantity of cells, if the aim was to produce patient-specific stem cells, so that immunocompatible cells would be available for all patients. And larger numbers of egg cells could only be donated by women who had undergone hormone treatment, a highly questionable procedure, not least because of the health risks.

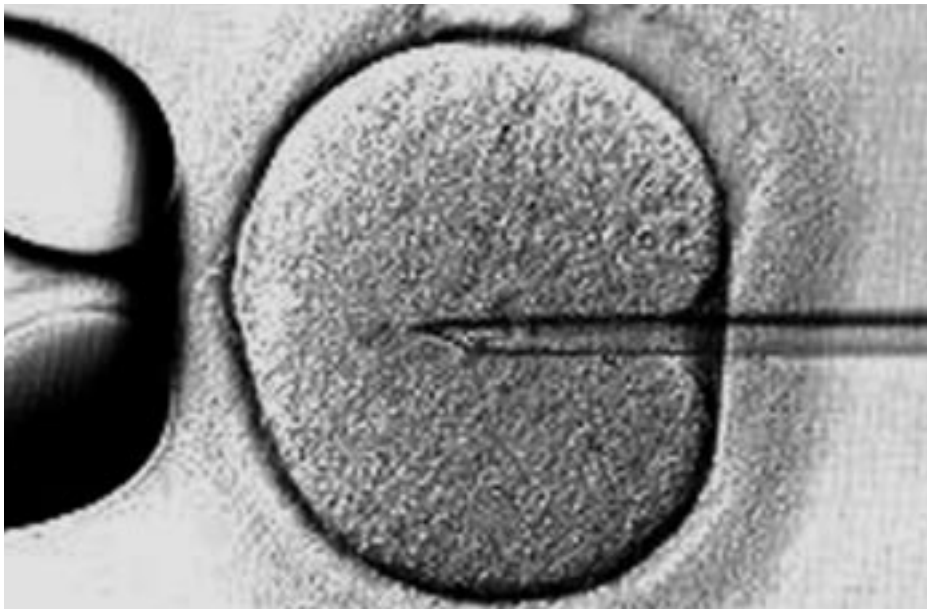
Many different views, no easy answers

Despite the wide range of opinions, there is at least unity in principle on two points. Firstly, there is consensus on the inviolability of human dignity and on the fact that respect for this dignity should be a guiding principle in our handling of this issue. Secondly, it is unanimously assumed that the embryo has its own value and is deserving of protection. However, opinions are divided on quantifying this value, and the degree of protection. Out of all the different views it is impossible to establish a «correct» position, even with such a far-reaching analysis of the relevant arguments. This is because depending on the basic philosophical and religious attitudes of the protagonists even contradictory viewpoints can be logically justified. It is the role of ethics to clarify the different viewpoints and their backgrounds. But if it is a matter of establishing a binding framework for stem cell research, taking into account the current level of information available and by applying generally accepted standards, then it is a matter for society.

«If we are in any reasonable doubt about whether we can or cannot do something that is technically feasible, it should be banned until all reasonable doubt has been removed.»
Johannes Rau

It all began with in-vitro fertilisation

It is more than 20 years since the first «test-tube baby» hit the headlines. When Louise Brown came into the world in 1978, it was an event sometimes described as the consequence of an inadmissible crossing of a line, as a symbol of scientists' obsession with feasibility. Today, the technique of in-vitro fertilisation (IVF) is medically routine and – especially in the USA – big business. Since 1978 some one million couples around the world have had their dreams of having children fulfilled after seeking medical help. However, this makes no difference to the fact that the success rate for in-vitro fertilisation is actually quite modest. This technique only helps one in every four or five women treated to have a child after just one course of treatment. In order to increase the success rate, for each treatment several egg cells fertilised in the test tube are generally transferred into the woman's uterus. It is also frequently the case that several treatment cycles are administered. Because a larger number of egg cells can only be obtained by subjecting the woman to a taxing hormone treatment, in many countries it is usual to fertilise as many egg cells as possible and to keep deep frozen those fertilised egg cells that are not used for the first treatment cycle for any subsequent cycles. This is one possible source for «superfluous» embryos, which at this stage are only a few days old, because if the woman becomes pregnant after only one treatment cycle and subsequently decides that she does not want any more children, or if she discontinues the treatment for other reasons, the deep-frozen embryos will be superfluous. There are tens of thousands of them all over the world. In Switzerland, since the beginning of 2001 there has been a ban on freezing fertilised egg cells for «stockpiling» purposes. The law on reproductive medicine only allows as many egg cells to be fertilised as can be implanted into the woman in one treatment cycle (maximum three). Only so-called «impregnated egg cells» may be stored deep frozen: in these cells, although the fertilisation has begun, nuclear fusion has not yet taken place. Such cells are therefore not regarded as embryos. But even this regulation, that is very strict compared to other countries, does not exclude the possibility that there will also be superfluous embryos in Switzerland in the future. This is because in rare cases a woman may withdraw from treatment at short notice, even if the fertilsed egg cells are ready for implantation, or she may become seriously ill or even die.



In-vitro fertilisation: in some cases, sperm cells are injected into egg cells (SINTEF Unimed)

The law sets the limits on research

The way a society deals with new technologies is influenced by cultural, historical and religious factors. In Europe, the debate about research on human embryonic stem cells is following a sometimes very different course. This also has an effect, not least on the legislative «crash barriers» that are imposed on this research in different countries.

The regulations that apply in different European countries to research on embryonic stem cells are very broad in their coverage, ranging from very liberal to extremely restrictive.

Liberal British regulations

British moral standards are of a strongly utilitarian nature, a point of view that assesses any action in relation to the greatest possible benefit for the public at large. Embryo research has been regulated in the UK since 1990 by the «Human Fertilisation and Embryology Act» (HFE Act). Under the HFE Act, research on human embryos can be approved up to the 14th day of their development by the competent authority, if the following research objectives are pursued:

- Advances in the treatment of infertility
- Furthering knowledge about the causes of hereditary diseases
- Furthering knowledge about the causes of spontaneous abortions
- Development of more efficient methods of contraception
- Development of methods for the identification of genetic or chromosomal abnormalities in embryos before implantation.

Following the announcement of the breakthroughs in research on human embryonic stem cells in 1998 referred to above, a proposal by the British government to extend the above catalogue of requirements was approved by the House of Commons at the end of 2000 and by the House of Lords at the beginning of 2001. Since then, on the basis of the therapeutic potential of stem cell technology, the following points also apply as grounds for the approval of research projects on embryos:

- Better understanding of embryonic development
- Better understanding of the causes of serious diseases
- Development of treatment possibilities for serious diseases.

The HFE Act permits – under certain conditions – both research on superfluous embryos from in-vitro fertilisation and also the selective production of embryos in the test tube for research purposes. The legal situation in the UK also allows the option of therapeutic cloning to be used for the harvesting of human embryonic stem cells. The British regulations are therefore among the most liberal in the world.

Current regulations of stem cell research in selected countries

	Reproductive cloning	Therapeutic cloning	Harvesting of stem cells from superfluous embryos
Germany	prohibited	prohibited	in principle prohibited*)
United Kingdom	prohibited	permitted	permitted
Switzerland	prohibited	prohibited	implicitly prohibited*)
U.S.A. private research	In most federal states: not regulated	In most federal states: not regulated	permitted
U.S.A. research founded by the state	prohibited	prohibited	prohibited*)

*) For details see text

Source: Commentary to EFG 20.11.2002

Strict regulations in Germany

Germany is one of the countries where the debate about research on human embryonic stem cells has been very intensive. It is centred on the discussion about the moral status and right to protection of the embryo. In Germany, there is widespread support for maximal protection of the embryo in vitro. This has also been voiced in the political debate, with the result that in April 2002, after discussing the issue twice, the Bundestag passed a law effectively prohibiting the harvesting of human embryonic stem cells. Only under very strict conditions does it allow exceptions for the import and use of these cells.

Below is a selection of these conditions stipulated under the German law on stem cells, which came into effect in July 2002:

- The stem cells must have been harvested prior to 1 January 2002 and the cell cultures must have been produced in conformity with the law in the country of origin.
- The stem cells must have been harvested from so-called superfluous embryos.
- The couple from whom the embryo comes must have given their free and informed consent to the use of the embryo for research and may not receive any rewards for it.
- Research projects on embryonic stem cells may be conducted only if they serve high-ranking research objectives and where there is no alternative way of achieving the desired gain in knowledge.
- Research projects on embryonic stem cells must be submitted to an interdisciplinary ethics commission for assessment.

The German regulations are among the strictest in the world. They have occasionally been criticised on the grounds that banning the harvesting of embryonic stem cells in Germany itself while permitting the import of such cells, albeit under strict conditions, is tantamount to double moral standards. This is countered by the argument that under the reference date criterion (see above) only cell cultures already in existence would be used, in other words no further embryos would be consumed.

«While scientists admit they are not yet certain, they believe stem cells derived from embryos have unique potential.»
George W. Bush

A middle way for Switzerland?

In the ethical and legal discussion about the protection or availability of embryos, it is important what parameters are set by the Constitution of the Swiss Confederation and under Swiss national law. For example, the 1997 international «Convention on Human Rights and Biomedicine», which the Swiss Bundesrat recommended to the Parliament for ratification – calls for indisputable boundaries and fundamental guarantees, including dealings with unborn life. More concrete parameters are set out in the second paragraph of Article 119 of the Constitution of the Swiss Confederation of 1999:

- Medically-assisted reproductive procedures may only be used where infertility, or the risk of transmitting a serious disease cannot be eliminated in any other way, but not in order to produce specific characteristics in the child or for research purposes; the fertilisation of human egg cells outside the body of the woman is permitted only under the conditions laid down by the law; only as many human egg cells may be developed into embryos outside the body of the woman as can be immediately implanted into her.
- All types of cloning and interventions on the genes of human germ cells and embryos are not permitted.
- Embryo donation and all types of surrogate motherhood are not permitted.
- No trade may be carried on in human genetic material and in products derived from embryos.

By its general ban on cloning, the Constitution of the Swiss Confederation also prohibits so-called therapeutic cloning in humans. This means that cell nuclear transfer for the purpose of harvesting embryonic stem cells is not permitted in Switzerland. The parameters set out in the Constitution are stated specifically in the law on reproductive medicine, which came into force at the beginning of 2001 (see table «The legal situation in Switzerland»). Only so-called «impregnated egg cells» may be deep frozen and stored, but fertilised egg cells – in effect early embryos – may not be (see box «In-vitro fertilisation»). The estimated 1,000 deep-frozen embryos still in existence from before 2001 may now be kept until no later than the end of 2003. Both the Constitution of the Swiss Confederation and the law on reproductive medicine leave open the question of whether such superfluous embryos may be used for research, for example for the harvesting of embryonic stem cells. To close this legal loophole, the Swiss Bundesrat has instructed the Swiss Federal Office of Public Health (BAG) to draw up a new law. A draft of this «Federal law on research on superfluous embryos and embryonic stem cells»– also referred to by its short name «embryo research law» (EFG) – was circulated between May and August 2002 for consultation to a broad group of individuals and agencies who are covering the relevant issues. In November 2002 the Bundesrat approved the revised bill and passed it on to the Parliament.

Under this bill, embryo research and the harvesting of embryonic stem cells will also be permitted in Switzerland. However, research may only be carried out on superfluous, artificially-fertilised embryos or on stem cells harvested from superfluous embryos. The stem cells may be sourced both internally and from other countries. The ban on the production of embryos for purely research purposes is to remain in the future, as is the import of embryos and therapeutic cloning. The bill sets out criteria that must be met before an application to carry out research on human embryonic stem cells can be approved (see box «Proposed regulations»). Should the proposed conditions come into force on schedule, the pre-2001 superfluous embryos referred to above could be used for research until the end of 2004, provided the stipulated criteria are met. Otherwise, the frozen embryos will have to be destroyed by the end of 2003 at the latest. Under the parameters set out in the bill, the only possibility for subsequent research will be to use the few embryos that become surplus to requirements for ongoing in-vitro fertilisation treatment cycles. In Switzerland this could mean a hundred or so embryos per year.

Legal situation in Switzerland regarding the harvesting of different types of stem cells

Origin of stem cells		Harvesting successful?	Legal situation in Switzerland
Embryonic stem cells	Superfluous embryos from IVF	Yes	To date: implicitly prohibited under EFG: permitted [1])
	Selectively produced embryos from IVF	Yes	Prohibited
	Cell nuclear transfer («therapeutic cloning»)	No	Prohibited
	Parthenogenesis	No	Implicitly prohibited
	Aborted embryos and foetuses	Yes	Permitted
Adult stem cells	Aborted embryos and foetuses	Yes	Permitted
	Umbilical cord blood	Yes	Permitted
	Bone marrow	Yes	Permitted

[1]) proposed regulation as per embryo research bill of November 2002

«Not even the noble aims of scientific research should be allowed to determine from what point human life should be protected.»
Johannes Rau

Proposed regulations for stem cell research in Switzerland

Given below are some of the provisions from the embryo research bill of November 2002, and also the criteria for research on human embryonic stem cells.

- Superfluous embryos may only be used for research purposes if the producing couples have given their approval freely and in writing after clarification.
- It is not permitted to allow superfluous embryos to develop beyond the 14th day.
- Superfluous embryos and embryonic stem cells may not be bought or sold for reward. They may be used for research only, but not for commercial purposes.
- The harvesting of embryonic stem cells is subject to the approval of the Swiss Federal Office of Public Health. Embryonic stem cells may be harvested only for specific research projects, or – if there is a need for them in Switzerland – for future projects.
- Only as many superfluous embryos may be used for the harvesting of embryonic stem cells as are absolutely necessary for the production of cell cultures.
- Research projects involving already harvested embryonic stem cells must be notified to the Swiss Federal Office of Public Health before they are carried out, and may only be started if the ethics committee responsible has given its approval. Such research projects may be carried out only if they comply with scientific quality standards and where equivalent results cannot be obtained in any other way.
- On conclusion of the research work, or after the harvesting of the stem cells, the embryos must be destroyed immediately.
- On conclusion or termination of the research work on superfluous embryos or embryonic stem cells, a summary of the research findings must be made available to the public.
- The import or export of embryonic stem cells is subject to authorisation.

Conclusions of the study

The regulations proposed in the bill on handling embryos are pragmatic. They set out criteria for the «utilisation» of superfluous embryos that are anyway doomed to die. Nevertheless, it would be highly desirable to broaden the discussion and thereby to keep an eye on research on all types of stem cells, as well as other cytotherapy options.

The many hurdles that have still to be overcome to establish cell treatments based on human embryonic stem cells seem to suggest that the time is not yet right to argue for the harvesting of such cells on a broad front. Moreover, it should be borne in mind that research on embryonic stem cells could also indirectly affect the ways and means in which other areas of biomedicine deal with human embryos. It is generally agreed that ethical and moral considerations should be given greater significance in embryo research than «purely» scientific and economic interests. But there are differing views on how binding regulations on embryo research should be worded, every one of which may well be justified in itself. The challenge for politicians and for society is to find a broadly acceptable solution in this sensitive area.