Aspects on properties, use and ethical considerations of embryonic stem cells – A short review

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Key words: embryonic stem cell, ethics, stem cell research

Abstract

Mammalian embryonic stem cells have the potential to differentiate into all cell types of an adult individual. The culturing of human embryonic stem cells renders possible studies that were previously only available in animal models. Embryonic stem cells constitute a particularly attractive tool for studies of self-renewal, commitment, differentiation, maturation and cell-cell interaction. There is currently considerable hope that studies of embryonic stem cells will lead to new therapies; either by themselves, through cell replacement strategies, or by generating results assisting other fields of research to reach clinical results. There are, however, considerable challenges to be met before embryonic stem cells can be used in large-scale clinical trials. Stem cell research is an area that has given rise to much debate internationally, within science, law and politics as well as within philosophy and ethics. The ethical attitudes expressed in the public debate over stem cell research notably divide over three important distinctions: (1) Reproductive versus therapeutic cloning; (2) Using already existing embryos versus producing new embryos for research purposes; (3) Production of embryos from eggs and sperm versus through somatic-cell nuclear transfer. The potential medical benefits that may result from embryonic stem cell research arguably support a continued development in this area. However, some opponents argue that this research offends the (relative or absolute) moral status of an unborn human. Furthermore, the research would probably prove to be a both time-consuming and very expensive method for treating disease. Thus, the questions arise whom the new technique would benefit and at what cost, if ever developed.

Introduction

Stem cells from embryos of non-human mammals have been known for two decades (Martin, 1981; Thomson et al., 1995; Evans and Kaufman, 1981). When it was discovered that such a cell type also exists in humans and can be cultured *in vitro*, a door to exciting medical breakthroughs was opened. Stem cells from human embryos have attracted enormous interest since the pivotal publication by Thomson et al. (1998) in the fall of 1998. This discovery has been accompanied by illustrations of frightening science fiction-like scenarios and intense debates about the true dignity of human life from conception to death. However, whilst the ethical and political discussions have been fierce,

the medical breakthroughs have so far been rather limited. Four years after the initial publication, we are still far away from initiating clinical trials, and research on embryonic stem cells remains a field in its early days of basic research. The reason for this relative lack of progress can in part be explained by limited availability of embryonic stem cells lines (Holden and Vogel, 2002), by national legislation prohibiting research with human embryos (Vogel, 2002a) and lack of funding (Rowley et al., 2002). Furthermore, patenting issues and secrecy may also have hampered the progress as there are several commercial biotech companies actively pursuing business opportunities within the stem cells field. Results from research performed in biotech companies will commonly not be a part of

the public domain until a patent has been filed. Thus, there might potentially be a considerable time lag between a discovery in a biotech company and public knowledge about the finding. Furthermore, results from biotech companies are often made public through press releases and only subsidiary through publication in peer reviewed journals.

As the intense public debate over stem cell research has made apparent, numerous ethical concerns accompany this new development, concerns that strongly influence the political, economic and legal contexts in which stem cell research is pursued. Scientific discovery coupled with technological innovation is essentially fraught with uncertainty, and the awareness of *potential risks* is particularly accentuated in countries where a relatively high level of general education render people more prone to claim their rights to information about and participation in the decision making processes. Transparency with regard to scientific facts, legal frameworks, commercialisation and political decision-making is a necessary condition for democratic control over scientific development. And such control can in its turn be a necessary condition for the successful introduction into society of beneficial novel technologies that public resistance might otherwise hinder. There are political problems involved when confronting risk and uncertainty. Furthermore, there is a complex legal framework that has to be acknowledged, present and emerging legal problems need to be addressed in national and international contexts.

Whilst advances in research on stem cells hold out promises for great future benefits, we need to bear in mind that the need for *regulating* the use of knowledge increases in proportion to its impact on society. Whether, in the area of stem cell research, it is possible to prevent abuse and ensure protection and morally acceptable (e.g., equitable) distribution of risks and benefits without hindering science from developing sufficiently to fulfil its promise is an important – and as yet open – question.

Biological aspects of embryonic stem cells

Embryonic stem cells can be derived from fertilised eggs in the following way. Approximately five days after fertilisation, when the fertilised egg has divided a few times, cells begin to differentiate forming a hollow sphere of cells called a *blastocyst*. The blastocyst has an outer layer of cells and an inner cluster of cells

called the *inner cell mass*. A few of the cells in this inner cell mass will develop into the foetus, whereas the rest will form extra embryonic tissue (including the placenta) needed for foetal development in the uterus. The cells in the inner cell mass that give rise to the foetus, are called *pluripotent embryonic stem cells* (commonly abbreviated ES-cells) since they can form every cell type in the body and are developed from the embryo. However, embryonic stem cells cannot form an organism because they are unable to generate the essential extra embryonic tissues (Thomson et al., 1998). Embryonic stem cell lines were isolated from mice in 1981 (Martin, 1981; Evans and Kaufman, 1981), monkeys in 1995 (Thomson et al., 1995), and humans in 1998 (Thomson et al., 1998).

In order to establish embryonic stem cell lines, the inner cell mass of blastocyst stage embryos is cultured in the presence of serum and on layers of murine feeder cells (Thomson et al., 1998). Human embryonic stem cells have a population-doubling time of about 36 hr and can be propagated for prolonged periods in serum free media supplemented with basic fibroblast growth factor (abbreviated bFGF). Animal as well as of human embryonic stem cells can be propagated without a change in the genetic constitution (karyotype) (Thomson et al., 1998; Odorico et al., 2001). This property is a prerequisite for extensive clinical use of embryonic stem cells. Another key characteristic is the maintenance of the chromosome ends and that undifferentiated human embryonic stem cells express high levels of the telomere regenerating enzyme telomerase (Lebkowski et al., 2001).

When human embryonic stem cells are induced to differentiate, they can develop into embryoid bodies (EBs) containing a high number of different cell types. Embryoid bodies resemble early stage embryos, but they are structurally highly disorganised compared to *in vitro* fertilised embryos and the morphology varies from one to another. The ability of embryonic stem cells to differentiate into a variety of cell types makes them valuable as a model system to study the mechanisms regulating lineage commitment and differentiation. In particular, this system enables detailed studies of early human development with regard to extrinsic and intrinsic regulators, as well as gene deletion/insertion studies.

Pluripotent stem cells are also found in the genital ridges of developing foetuses and have been derived from 5–9 weeks old aborted human foeti (Shamblott et al., 1998). These cells are commonly termed embryonic germ (EG) cells. Although pluripotent stem

cells exist in embryos and developing foeti it is presently unknown whether such cells also reside in new borne and adults. However, recent results might indicate such a finding (Jiang et al., 2002).

Embryos can also be generated by somatic cell nuclear transfer (SCNT; also called therapeutic cloning). SCNT is performed by removing the nucleus of an unfertilised egg (enucleation) and replacing the nucleus with the nucleus of a somatic cell from another person. The egg containing the transferred nucleus is then stimulated to divide until it reaches the blastocyst stage, at which time the cells of the inner cell mass can be removed and embryonic stem cells derived. No currently published report claims to have been successful in establishing human embryonic stem cell lines from blastocysts generated by somatic cell nuclear transfer (Cibelli et al., 2002a). Embryos generated by SCNT are genetically identical to the person donating the nucleus in regard to the chromosomes. The egg donor contributes however also with DNA since the mitochondrion, which resides in the cytoplasm, also will be a part of the developing embryo. Thus the embryo is not 100% identical to the person donating the nucleus, unless it is the same person donating both the egg and the nucleus.

Embryonic stem cells and clinical trials

There is considerable hope that embryonic stem cells can be utilised in the treatment of a wide range of human disorders. A complete lack, or a deficient number of different types of cells causes various diseases. To illustrate: a lack of certain types of nerve cells may cause Alzheimer's and Parkinson's diseases, stroke patients lack functional heart muscle cells in particular regions; lack of specific types of blood cells can be found in patients with immune deficiencies and anaemia; whilst lack of insulin-producing cells will lead to type I diabetes. These are just a few amongst many diseases theoretically treatable by stem cell-aided interventions. A number of clinical trials with adult as well as foetal stem cells are presently ongoing. Clinical trials with embryonic stem cells from embryos have however not yet begun.

It is expected to take many years before embryonic stem cells will enter large-scale clinical trials. For example, much effort is currently being put into developing efficient systems for establishing and culturing embryonic stem cells in the absence of serum or other animal derived factors (Xu et al., 2001). A defined culture system, free of animal proteins and/or cells is

needed to eliminate the risk of transmitting animal viruses and other disease causing agents (xenozoonoses) through the culture system. Consequently, if only human cells that have never been in contact with animal cells are allowed to be used in clinical trials, the currently available embryonic stem cell lines are unsuitable, since all of them have been in contact with murine feeder cells.

Extensive animal experimentation is required in advance of any clinical trial. One important objective in animal studies is to evaluate potential toxic side effects. However, toxic side effects of human embryonic stem cells (or derived cells thereof) can only to a limited extent be observed in animal models. This is due to the expected rapid immunological elimination of human cells in immune competent animals and limited physiological responses due to species differences. It follows that unless animal model systems are developed that highly resemble the planned clinical trial, animal studies will only be of limited value to predict toxic side. The decisions on what types of animal experiments are required before clinical trials are likely to be made on a case-to-case basis. The complexity of the required animal studies will depend on the type of patients being tested as well as the ability to remove the transplanted cells if unwanted side effects should appear.

Undifferentiated embryonic stem cells represent a high risk of developing cancer when transplanted into immunocompromised patients. Thus, if undifferentiated embryonic stem cells are being used it might be necessary to develop recall mechanisms or, alternatively, make sure that only differentiated cells are being transplanted to avoid the risk of cancer formation in the recipient.

Immunological rejections

Any transplantation must be tailor-made in the sense that the recipient's immune system must tolerate the transplanted cells and thereby not reject the graft. In regard to stem cells, this challenge can potentially be overcome by a variety of strategies. The options used today are the use either of the patient's own cells, of cells of a related person, or of cells from an unrelated donor. In the future, embryonic stem cells suitable for transplantation can theoretically be obtainable by a variety of means, including the establishment of large banks of embryonic stem cells that would enable the selection of cells; notably, the immunologically best fit stem cell for the patient in question (Vogel,

2002b). Embryonic stem cells can also theoretically be tailor-made to an individual patient by somatic cell nuclear transfer (therapeutic cloning), or by sophisticated methods for 'transplanting' human leukocyte antigen (HLA) -regions from the patient's genome to embryonic stem cells. Furthermore, it is theoretically possible to generate 'universal' embryonic stem cell lines by, for example, removing the genetic components that trigger the immune system of any (or: most) human recipient(s). Another method is called parthenogenesis (virgin birth) and has been proposed as an alternative strategy to generate transplantable cells that are compatible with the recipient's immune system (Cibelli et al., 2002b). Strategies to modulate the recipient's immune system in a way that the desired cells are not being rejected can also be proposed.

Differentiation potential

Humane ES-cells have demonstrated their potential to differentiate into cells of all three germ layers (ectoderm, mesoderm and endoderm) (Thomson et al., 1998; Itskovitz-Eldor et al., 2000). Notwithstanding, only a limited amount of data is available concerning their potential to differentiate into cells of a particular lineage in sufficient amounts to envisage a clinical usage. This is partly in contrast to murine embryonic stem cells, which has been studied more extensively and demonstrated to differentiate into a number of various cell lineages. Furthermore, experimentation with non-human primate embryonic stem cells has demonstrated physiological effects in various animal experiments (Klug et al., 1996; Yamashita et al., 2000; Potocnik et al., 1997; Liu et al., 2000; McDonald et al., 1999; Lumelsky et al., 2001; Kim et al., 2002). However, it has recently been shown that even human embryonic stem cells can differentiate with some degree of specificity into endothelial (Levenberg et al., 2002), nerve (Schuldiner et al., 2001; Zhang et al., 2001) and hematopoietic cells (Kaufman et al., 2001). These results support their proposed extensive clinical usefulness.

A short review of some ethical problems involved in stem cell research

Embryonic stem cell research is an area that has given rise to much discussion internationally, within science, law and politics as well as within philosophy

and ethics. The ethical concerns that accompany this new development are numerous and strongly influence the political and legal contexts in which stem cell research may or may not continue to develop. In some countries, such as the United States, there are strong calls for a general ban on research involving the use of human embryos (Annas, 2002). In contrast, the prevalent attitudes in other countries (for example, Sweden, France and the United Kingdom) favour a more liberal and diversified position, to be described below.

The debate around stem cell research is not always clear, or even well informed. It is an area, in which it can be difficult to know *towards what*, exactly, our ethical attitudes are directed. The facts and the technical terminology are complex, and the development is rapid, especially from a layman's point of view. Cloning is an ambiguous concept, in the sense that we must distinguish between, on the one hand, 'reproductive' cloning and, on the other hand, 'therapeutic' cloning. Therapeutic cloning has furthermore other names, as some authors prefer to use the term 'research cloning', or 'somatic nuclear transfer'. One reason is that the word 'therapy' indicates current therapeutic potentials and that the term 'cloning' has become so emotionally loaded. Furthermore is the concept of stem cells not one that all participants in the debate clearly understand, or necessarily use in the same sense.

In the numerous discussions of ethical problems concerning stem cell research, the following three distinctions are amongst the most relevant ones to bear in mind:

1. *Reproductive* versus *therapeutic* cloning.
2. Using already *existing* embryos versus producing *new* embryos for research purposes.
3. Production of embryos from *eggs and sperm* versus through *somatic-cell nuclear transfer*.

Some of the many ethical questions that are often raised concerning the development of human stem cell research will here be presented in terms of these distinctions.

Reproductive versus therapeutic cloning

Most organisms can be individuated by their genetic structure. A clone, in contrast, is a genetic copy of the chromosome-donor (Brem, 1997). Sperm are superfluous in the context, and in so far as the cloned organism grows in and is born from a womb, it in-

herits few genetic properties from that female. The chromosome-donor (male or female) determines most of the clone's genetic properties. Genetically indistinguishable organisms exist already in nature as so-called 'identical' twins.

Ever since a group of British embryologists published an article revealing that they had successfully cloned a mammal, a sheep called Dolly (Wilmut et al., 1997), cloning has been hotly debated amongst scientists, politicians and the general public (New York Times, 1997). One frequently expressed worry with respect to the possibility of cloning human beings is that it would produce 'xerox copies' of living organisms. Fearfully, one envisions an army of indistinguishable individuals: *homo xerox*. This particular concern is based on a misunderstanding of the type of identity-relation which cloning involves: the false belief that cloning produces individuals that are totally identical, physically as well as mentally (Evers, 1999). Who, or what, someone or something is, is also a far more complex subject than mere genetics (Der Spiegel, 1997). More serious objections against reproductive cloning concern the health of the cloned individual, the social reception and subsequent life of the cloned child, and the fact that the reasons for wanting to clone a child in the first place may be morally unacceptable. All human beings should, following a classical tenet, be considered as ends in themselves and never merely as means to an end, and to experiment with the production of cloned human beings is ethically dubious. Today, there are very few politicians or scientists who consider reproductive cloning of human beings morally acceptable. Reproductive cloning is banned in all countries in the world that have legislation on this issue. However, many countries do not.

Regarding therapeutic cloning, the attitudes are far more diversified. There is a great variety of positions. Unlike reproductive cloning, therapeutic cloning holds promises for possible medical use, e.g., the treatment of currently incurable diseases, as described in the previous section. The Opinion of the European Group on Ethics in Science and New Technologies to the European Commission No. 16, states that '*it is thought probable that stem cells will find use in the therapy of degenerative diseases or injuries. Other potential applications for human stem cell cultures include uses for drug design*' (The Opinion of the European Group on Ethics in Science and New Technologies to the European Commission, 2002). Because of those possibilities, many people regard therapeutic cloning as

acceptable, something that should be explored to develop new or better treatment for disease, and even as a '*duty of solidarity towards future generations*' (Petit-nicolas and Perez, 2002), provided that it is carefully regulated to prevent abuse.

In contrast, some people are as negative to therapeutic cloning as they are to reproductive cloning, either because they hold a general view (often but not necessarily religiously based) that any use of human embryos in research is as such unacceptable, or because they fear that, whilst there may be moral differences between the two techniques, the former would open the door to the latter. The latter objection could possibly be countered by imposing sufficiently strict rules for the handling of human embryos and stem cells that would hinder such a 'slippery slope' development. However, such regulations must then be backed up by a body of control, making sure that the regulations are actually respected, thus gaining (and meriting) public trust. The anxiety people feel about the rapid development of science should not be seen as a mistrust of science exclusively, but also as a mistrust directed against the institutions whose responsibility it is to regulate these advances. The former objection appeals to the status of human embryos and stem cells, which requires careful consideration. The issue concerns the beginning of human life, from what stage of its development a human embryo enjoys protection, and if this protection from a given stage is relative and gradual, or absolute, i.e. not a question of degree.

Using already existing embryos versus producing new embryos for research purposes

The extreme position, most often advocated in the United States, that embryos enjoy absolute protection in the earliest stages of their development and cannot be destroyed for any reason or used for research purposes regardless of the potential use of the latter, is quite uncommon in Europe and Asia. It is a position that is to a large extent religiously based. Liberal abortion policies limit the rights of the embryos in many countries, conceding them only relative protection. In Sweden for example, the embryo/foetus growing in a female body has no right to life for the time specified in the abortion law, which posits the unconditioned right of the woman to terminate pregnancy within a given time frame. This is not subject of political debate but regarded as a fundamental human right of women. An aborted foetus can be used in research given the informed consent of the mother and permission from

the Swedish National Board of Health and Welfare, which can only be given if there are no acceptable, less invasive methods for reaching similar results. (In order to use embryos, that are left over and destined to be destroyed the informed consent of both donors is required (Vogel, 2002c)). Numerous governments, e.g., in Sweden, The Netherlands and France, either accept or recommend the acceptance of fertilised human eggs as a source of stem cells (Table 1).

In other countries, e.g., Germany and Norway, the current legislation allows abortion, but prohibits research on fertilised eggs. The legislation regarding embryonic stem cell research in Norway was recently changed to specifically ban both the derivation and use (including import) of embryonic stem cell lines (The Norwegian Ministry of Health, 2002).

Recommending the use in research of already *existing* human embryos – for example, the use of spare *in vitro* fertilisation embryos, anyway destined to perish – is not tantamount to allowing the creation of *new* human embryos for research purposes. Amongst those who do accept the use of existing embryos, not all accept the production of new embryos for research purposes. The latter could be considered more active, and the embryo created exclusively for research purposes would not be seen as an end in itself but merely as a means to an end, thus breaking the above-mentioned moral tenet. The French National Consultative Ethics Committee advocates ‘controlled possibilities for the use of spare IVF embryos for research purposes, in particular research on embryonic stem cells’, adding a ‘firm reminder that creation of human embryos for purposes of research is prohibited’ (Paris: Comité Consultatif National d’Ethique, 2001). Pragmatically, the number of supernumerary fertilised eggs is likely to be sufficient to support stem cell research for several years.

An ethically relevant difference should be noted here between *stored* and *freshly made* eggs. Storing creates spatial/temporal distance that is absent if freshly supernumerary fertilised eggs are allowed for research. This makes a psychological, emotional and practical difference when discussing the availability of supernumerary fertilised eggs. In Norway the discussion has solely been focused on the use of IVF embryos set to be discarded at the end of the allowed three-year storage period. In Sweden, in contrast, it is allowed to use freshly fertilised eggs for stem cell research. Such a scheme necessitates a strict system to avoid eggs being ‘unintentionally’ fertilised only for research.

Production of embryos from eggs and sperm versus through somatic cell nuclear transfer

Embryos can be produced in different ways: they can be produced from sperm and eggs, but they can also be produced through somatic cell nuclear transfer (Weissman, 2002). Numerous countries, such as Belgium, Sweden and the United Kingdom have decided or recommended that the latter method should be accepted. However, acceptance of the production of embryos through nuclear transfer does not entail acceptance of the production of embryos from sperms and eggs. In Sweden, for example, the Swedish Research Council rejects the production of embryos from eggs and sperm arguing that there are ‘less invasive’ methods for acquiring embryos, but recommends the creation of embryos for research purposes through somatic-cell nuclear transfer.

Permitting somatic nuclear transfer for the production of stem cell lines is not necessarily the same as allowing the production of potential human beings for use in research. Furthermore, it can theoretically be envisaged that unfertilised eggs can be replaced by other cell types enabling the generation of embryonic stem cell lines without concurrently generating the ethically controversial blastocyst. However, if the production of human pluripotent stem cell lines by the use of somatic nuclear transfer does not imply the creation of embryos that could develop into fully grown individuals – do the reasons for prohibiting or limiting their creation for research purposes remain? Is it only the potential infant, nascent life, which should be protected?

For some groups, mainly in the United States, ‘blastocysts produced by nuclear transplantation are embryos to be accorded full human rights, and their destruction to produce embryonic stem cell lines constitutes the taking of lives’ (Weissman, 2002). For other groups throughout the world this is not reasonable. According to them, the rights of embryos are not absolute, but should be determined in relation to their origins and potential use. If the embryonic stem cell lines are produced according to strict regulations to prevent abuse, and for medical purposes that might positively, in a health-related manner ‘affect hundreds of thousands of lives’ (Weissman, 2002), it does not seem morally acceptable to prevent the production of blastocysts by somatic nuclear transplantation for this reason.

Yet there are other reasons to consider. Whether or not we consider the blastocyst an embryo, and whether

Table 1. Legislation – Use of embryonic stem cells in research

	Use of supernumerary fertilised egg	Fertilise eggs solely for stem cell research	Therapeutic cloning	Import of ES-cell lines
Australia	+	–	–	+
Canada	+	–	–	+
China	+		+	+
Denmark	–	–	–	
Finland	+			+
France	–	–		
Germany	–	–	–	+
Iceland	–	–	–	
India	+			
Ireland	–	–	–	–
Israel	+	–		+
Italy	–	–	–	–
Japan	+		–	+
Norway	–	–	–	–
Singapore	+		+	+
Spain	–	–	–	–
Sweden	+	–	–	+
The Netherlands	+	–	–	+
United Kingdom	+		+	+
U.S.	+		+	+

‘+’ = Allowed; ‘–’ = Not allowed.

Discussions related to legislative issues regarding embryonic stem cells are ongoing in many countries (Vogel, 2002a, c; Dennis, 2002; European Commission, 2002). Thus, this table is expected to be outdated in the near future. It is important to note that although a country allow certain types of embryonic stem cells research there are commonly a comprehensive list of requirements needed to be fulfilled before such research may start.

or not we concede an embryo absolute right to protection, there are independent reasons for scepticism towards the use of therapeutic cloning. Notably, there are *economical* considerations (Evers, 2002). As yet, therapeutic cloning has not successfully been carried out on human beings, and, if developed, it could prove to be a both time-consuming and very costly method for treating disease. It is, of course, difficult to assess today the likely costs in the future. Nevertheless, hypothetically, if the costs prove to be very high, research funding could arguably be used more efficiently in the aim of finding cures for (notably, poverty-related) diseases that presently affect a considerably greater number of people on the planet than those whom therapeutic cloning might cure. Furthermore, there is a risk that the global distribution of benefits would be unfair: would this be yet another medical advance developed at high cost by and for the developed countries? It does not appear likely that therapeutic cloning would primarily benefit the populations in developing countries where there are much

more urgent diseases to fight, such as HIV or malaria. Indeed, by the previous argument, the developing countries will be disadvantaged because the available funds will be directed towards developing this new technique rather than towards helping them find cures (or receive existing cures) for their illnesses.

Conclusion

Embryonic stem cells provide a potential powerful *in vitro*-model of early human development. Embryonic stem cells can be used within basic research as well as within drug discovery. Advanced *in vitro*-systems, set to mimic early human development and complex cellular interactions could additionally facilitate the discovery of blocking/stimulatory factors affecting various cells/tissues in normal as well as pathophysiological model systems.

However, it is difficult to predict the future usefulness of embryonic stem cells for treating currently incurable human diseases on the basis of their value as a

tool in basic research. As mentioned above, there are a number of hurdles that need to be solved before large-scale clinical trials with embryonic stem cells can be started. Amongst the greatest technological challenges we find issues related to immunocompatibility, recall mechanisms, xenozoonoses and the task of generating sufficient amounts of the required physiological responsive cell type at the appropriate site *in vivo*. Due to the number and severity of the technological challenges remaining to be solved before the initiation of large scale clinical trials, embryonic stem cells are not likely to be a part of routine clinical practise in the foreseeable future. Their immediate usefulness is therefore likely to be limited to basic research and *in vitro*-model systems.

Furthermore, even granted that this new technique does hold out promises for future medical benefits, and that these appear reasonably accessible scientifically speaking, the ethical-social questions arise: Whom would they benefit, and at what cost? Will these benefits really be worth their price within a national and global health-perspective?

Amongst the main ethical arguments presented in this chapter, one is in favour of the development of stem cell research into clinical applications, whereas three are in different ways sceptical towards its value, or justification. Our account has primarily been descriptive; a full evaluation is beyond our present scope and purpose. Amongst the three objections, the first comes in numerous versions of varying strength, and the last two are closely connected.

- (1) *Pro*: In view of the obvious medical benefits that may result from this new technique, such as finding cures for presently incurable diseases, e.g., Parkinson's or Alzheimer's, do we have the right not to develop it further?
- (2) *Contra*: The use of embryonic stem cells challenges the moral status of unborn humans (as an embryo or blastocyst produced from eggs and sperm or through somatic-cell nuclear transfer, and as fully developed foeti).
- (3) *Contra*: The technique could be expected to involve high costs. If so, it is difficult to justify the use of such large funds that could arguably be better used, e.g., to treat diseases that affect a greater number of people than those whom the development of stem cell research could be expected to cure.
- (4) *Contra*: The global distribution of benefits is likely to be unfair. The populations in developing

countries have more urgent diseases to fight, and will be disadvantaged if large parts of the available funds are directed towards developing this new technique rather than towards helping them in this quest.

Most countries performing medical research have, or will in the near future discuss, legislative and funding issues related to research on embryonic stem cells. The use of supernumerary fertilised eggs, fertilisation for the sole purpose of research, therapeutic cloning and import of embryonic stem cell lines are all controversial issues. As depicted in Table 1, several countries allow the use of supernumerary fertilised eggs for stem cells research, whereas only a few allow therapeutic cloning and fertilisation solely for research. Others have taken a more pragmatic approach by allowing import of embryonic stem cell lines, given certain conditions, whilst not allowing generation of new cell lines. On the one hand, the latter approach can easily be criticised for institutionalising dual standards and double-morality. On the other hand, it enables a step-by-step approach to an ethically controversial, but still promising, field of research. The currently available embryonic stem cell lines might not be sufficient to explore the full potential of these cells (Holden and Vogel, 2002). However, the stem cell lines available will surely give some insight into whether or not embryonic stem cells have a clinical potential or that their usefulness will be restricted to basic research and potential drug discovery.

It will presumably take many years before embryonic stem cells demonstrate a true usefulness in clinical trials (if they ever will). Nations preferring a restrictive legislation is therefore not likely to be challenged by breakthroughs in clinical trials in the near future. This is not to deny that it is nearly impossible to predict the future status of embryonic stem cell research on, say, a 20 yr horizon and determine whether or not a restrictive legislation will in fact be challenged by such breakthroughs.

There seems to be broad international agreement that a world-wide ban on reproductive cloning would be justified. However, such a ban might be challenging, maybe even impossible, to issue because it is difficult to formulate it without automatically blocking the development of non-reproductive (therapeutic) cloning, over which attitudes are far more diversified. Oppositions arise, notably, from differences in attitudes concerning the status of embryos and varying conceptions of human dignity. Many people who

are against reproductive cloning are in favour of embryonic stem cell research and of allowing therapeutic cloning, whereas others want to ban both. Yet others can support a restrictive legislation on embryonic stem cells research with the arguments that other avenues of research are even more promising.

A legislation that restricts embryonic stem cell research and limits its funding would arguably prolong the path to new treatments for presently incurable diseases. However, this argument could be reversed: if embryonic stem cell research receives fewer funds, other strategies for curing the same (and perhaps other) diseases can receive more financial support. It is not self-evident that these alternative strategies may not reveal even better results, as it is difficult to predict the future usefulness of embryonic stem cells.

Acknowledgement

We thank Sissel Rogne, Øyvind Baune and Steinar Funderud for critically reviewing the manuscript.

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