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viewpoint

The future of stem-cell research in Germany

A Delphi study

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The controversial issue of stem-cell research encompasses a truly interdisciplinary field that involves not only various scientific disciplines, but also medical, ethical, political, legal, societal and economic aspects. It is no surprise then that this research—in particular when using human embryonic stem cells (hESCs)—has led to an intense debate about the possible medical and economic benefits as well as the ethical and societal problems of using human embryos in biomedical research. These debates have affected various countries, most notably the USA and Germany, and have led to different legal regulations and limitations of stem-cell research.

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We have conducted a study among leading German stem-cell experts on the future of embryonic and adult stem-cell research in this country to assess its scientific, therapeutic and social prospects. It revealed that, in addition to ethical problems, different expectations about the scientific and therapeutic prospects of embryonic and adult stem-cell research account for the current German preference for adult stem cells. Nevertheless, the majority of German experts expect an increasing open-mindedness towards embryonic stem-cell research in this country, as well as a relaxation of legal restrictions.

Based on their origin, stem cells are broadly categorized into either adult (syn. somatic), or embryonic stem cells. Both cell types can—to different degrees—differentiate into various specialized cells and tissues, which has created considerable scientific and medical interest. Biologists in basic research hope to gain insight into the fundamental processes of human cell development, whereas biomedical researchers want to use stem cells to replace failing cells, and eventually whole tissues, as a therapy for various—as yet incurable—diseases. Although the current discussions mainly revolve around therapeutic applications, it is important to note that stem-cell research is, for the most part, still at the stage of basic research. One exception is the transplantation of adult stem cells for the recovery of the blood-cell system in leukaemia therapy. In addition, recent findings seem to indicate that human adult stem cells (hASCs) taken from bone marrow can improve cardiac function in patients after acute myocardial infarction (Wollert *et al*, 2004).

Whereas discussions about using hASCs are less controversial, research on hESCs has stirred German society and politics (Colman, 2001; Matthiessen-Guyader, 2003; Mieth, 2000; Oduncu, 2003). This is, in fact, not limited to Germany; other countries—most notably the USA and the UK—are actively discussing various legal and ethical aspects. These controversies do not arise from the use of hESCs, but from their acquisition—they must be obtained from a 5- to 7-day old blastocyst, which inevitably leads to destruction of the embryo. The ethical debate involves several lines of argument; the central issue, however, is the moral status of the embryo. Two positions are predominant in Germany: one grants the embryo absolute protection from its inception, whereas proponents of a graduated protection of life take other, therapeutic, goals into account. Denying the embryo any moral protection is a position that is rarely found in Germany (Nationaler Ethikrat, 2002; Enquete-Kommission Recht und Ethik in der modernen Medizin, 2002).

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Among the proponents of a graduated protection of life, further debates focus on the balance between the freedom of research and the potential of future therapeutics, against the protection of the early embryo. In this context, two questions are of acute concern. How can the treatment of embryos in different contexts, such as stem-cell research versus induced abortion, be justified? The second question concerns the perceived moral double standard behind allowing the import of

hESC lines while prohibiting their production in Germany. Naturally, the freedom of research has an important role in academic and scientific circles, whereas promises of potential treatments are of much higher relevance to the public debate. At the heart of the debate about hESC research in Germany is the difficulty in finding a proper and socially acceptable balance between protecting the embryo for moral reasons, enabling therapeutic prospects for patients suffering from incurable diseases, and protecting freedom of research.

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As noted before, the production of hESC lines is currently illegal in Germany; the 1990 Embryo Protection Act prohibits any utilization of the embryo that does not serve its preservation. However, although the act makes the use of human embryos for research purposes a punishable offence, it does not explicitly prohibit the import of hESCs. The German Parliament made use of this loophole to establish the 2002 Stem Cell Act, which allows the import of hESCs for high-ranking research objectives. These must be evaluated by the Robert Koch Institute, a federal institute in Berlin, and its central ethics committee for stem-cell research (www.rki.de). Moreover, only hESC lines produced from surplus embryos from *in vitro* fertilization (IVF) before 1 January 2002 can be legally imported. This key date was chosen to ensure that no hESC lines are directly produced for German research; in other words, that no human embryos are destroyed 'on German order' (Bundesärztekammer, 2002; Matthiessen-Guyader, 2003). By 31 December 2003 seven applications were under consideration from which five have already been accepted (Bundesministerium für Bildung und Forschung, 2004). These focus on the differentiation of hESCs into either neural (progenitor) cells or cardiomyocytes. In addition, procedures for harvesting and characterizing cells are of major interest.

German legislation of stem-cell research is more restrictive than that found in most other European countries and the USA (Hüsing *et al*, 2003; Enquete-Kommission, 2002; Bundesärztekammer, 2002). Finland, Greece, the Netherlands, Sweden and the UK allow the production of hESC lines from surplus IVF embryos. Cloning of embryos to produce stem-cell lines for therapeutic purposes is legally permitted only in the UK, where, in accordance with the 1990 Human Fertilisation and Embryology Act, only embryos younger than 14 days can be used. Although research proposals in the UK must be accredited by the Human Fertilisation & Embryology Authority (www.hfea.gov.uk), the prerequisites for attaining a licence to conduct research with hESCs are less strict than in Germany. By contrast, Ireland, Austria, Denmark and France prohibit any production of hESC lines. In the USA, research with hESCs is not prohibited, but scientists can only use cell lines produced from surplus IVF embryos created before 9 August 2001 if their research is financed with federal funds. Privately funded research on hESCs or the production of hESC lines is not regulated by federal law.

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If a graduated protection of the embryo is the predominant position in most countries, lawmakers have to take into account different values. To enable a balanced consideration of freedom of research, therapeutic prospects and the moral status of the human embryo, it is therefore necessary to clarify the current status and the potential of stem-cell research. Thus, we conducted an in-depth expert Delphi study to explore the future of stem-cell research in Germany. The two-phase study began in June 2003 and was completed in May 2004. The study focused on developments in fundamental research and therapeutic applications as well as on societal, political and legal frameworks, but also took into account effects on related fields of research.

The Delphi method is a technique that supports and structures group communication processes on complex problems through a panel of geographically dispersed experts (Linstone, 1975; Adler & Ziglio, 1996). It was developed in the early 1950s by Olaf Helmer and Norman Dalkey at the RAND Corporation—a non-profit research organization in Santa Monica, CA, USA—to help strategic military planning (Gordon & Helmer, 1964), but was soon adopted for civilian purposes. It is now widely used in many countries to generate forecasts in research and technology.

In the beginning, a team must be assembled to conduct and monitor a Delphi study on a given subject. This team selects the experts to participate in the study and develops the questionnaire. After the experts have completed the questionnaires, the relative frequencies of the answers are then incorporated and questions may be refined or added. The revised questionnaire, with the opinions of all experts from round one, is then sent back to the participants to be filled out at least once more. The repeated application of the questionnaire is meant to enable the experts to refine their views when confronted with the results of the whole panel. This process can be reiterated to achieve stability in the results, but most Delphi studies consist of only two rounds of questioning. When the last round of the study is finished, the responses are analysed and the team prepares a report on the analysis and the conclusions of the exercise (Linstone, 1978).

Our questionnaire consisted of 57 statements describing future developments for stem cells in fundamental research, therapeutic applications, societal, political and legal frameworks and related fields of research, such as cloning, IVF and toxicology. The statements were adopted from relevant publications (National Institutes of Health, 2001; National Academy of Science, 2002; Hüsing *et al*, 2003; Commission of the European Communities, 2003) and were evaluated regarding the following criteria: timeframe of realization (in five-year steps until 2023); desirability; risks and opportunities for patients, research and industry; and the most important factors of influence. Desirability was chosen to assess whether the experts believe that certain developments are desirable or not. Factors of

DESIGN OF THE DELPHI STUDY ON STEM-CELL RESEARCH IN GERMANY

The central element of the Delphi study that we conducted among German stem-cell experts consists of a number of statements. These statements were descriptions of possible future developments in stem-cell research that had to be judged by the experts. The following text is an excerpt from the questionnaire with statements from the four main fields of interest.

Basic research

•Efficient methods have been established to produce and enrich various tissue-specific human adult stem cells.

•The processes that allow the re-differentiation of tissue-specific stem cells into pluripotent stem cells are known.

•Human embryonic stem cells can be cultivated for a period of at least 15 years and have been successfully differentiated.

•Human embryonic stem cells can be differentiated and enriched so as to produce the desired cell type in large quantities.

Therapeutic applications

•Parkinson's disease can be cured by implanting human embryonic stem cells into the patient's brain.

•Alzheimer's disease can be cured or halted by using human stem cells in various areas of the brain.

•Insulin-producing human adult stem cells are successfully used to treat diabetes.

Social framework

•The public debate about the ethical aspects of embryonic stem cell research has led to amplified funding of adult stem cell research.

•Due to medical successes, the use of human embryonic stem cells is accepted by the majority of the population.

•Due to the public debate about the risks and ethical problems of embryonic stem-cell research, more than 50% of the German stem-cell researchers have left Germany.

•International guidelines for biomedical research *de facto* prohibit research on and the use of human embryonic stem cells.

Consequences for other fields

•The broad application of stem-cell therapies leads to a reduction of the most prevalent diseases, such as coronary heart disease and infectious diseases in Germany.

•The number of kidney transplants decreases continually because early use of cell therapies in metabolic and organ diseases can prevent kidney failure.

•Therapeutic cloning is increasingly used in medical practice to produce human embryonic stem cells specific for the patient for cell therapies.

•The number of experiments using animals in toxicological and pharmaceutical research has been reduced by 30% through the use of human stem-cell lines.

By checking boxes, the participants had to comment on how good their specific knowledge about the relevant statement was. A second column asked them if and when they believe the development described in the statement will be realized and a third whether they think that this is a desirable development. Another column asked them what risks and/or opportunities they anticipate for patients, publicly-funded research and private research.

A final column asked for social, economic, political and scientific factors that could have an influence on the realization of these developments. These factors are: public funding, private funding, scientific personnel and education, efficient technology transfer between universities and industry, national (German) and international markets, social acceptance, publicly-available information, international cooperation, political and legal frameworks as well as private and public health insurance. The participants could select three factors that they thought to be most important for realization.

influence describe various aspects that could play a role in future directions of stem-cell research both scientifically and socially (see sidebar).

Using literature research and consultations, we identified 110 leading German scientists who work in basic or applied stem-cell research, or in research on the ethical, societal and legal aspects of stem-cell research. Of those, 49 took part in the first round of our Delphi study and 36 in the second round. The majority of the participants (63.7%) work at universities, 27.6% at research institutes and the remaining 8.7% in industry. More than 60% work in basic research, almost 40% in applied research, about one-fifth in clinical practice and about one-sixth focused on the ethical, societal or legal aspects of stem-cell research. To avoid any bias, the number of scientists was balanced in regard to their focus on adult or embryonic stem cells as well as on human versus animal stem cells. After an analysis of the answers, the same questionnaire—this time including the relative frequencies of responses in round one—was sent back to the experts to be assessed once more.

The results of the second round revealed large differences between adult and embryonic stem-cell research in regard to the desirability of certain developments, as well as their predicted timeframes of realization. In general, the desirability of all developments in ASC research was on average about 25% higher than the comparable values for ESC research. Moreover, 40% of the experts doubt that major risks with embryonic cells, such as tumour development and false differentiation of transplanted cells, could ever be ruled out. It seems that these major therapeutic problems, in addition to ethical concerns, are mainly responsible for the current German focus on ASCs and scepticism concerning the use of ESCs.

The experts are quite optimistic regarding developments in ASC research. Almost 90% expect the establishment of efficient methods for the extraction and accumulation of various kinds of ASCs within the next ten years and the possibility of reprogramming ASCs into a pluripotent state within the next 15 years. By contrast, advances in ESC research are assessed more cautiously and have a higher risk of failure. For instance, although the precise differentiation and purification of hESCs is anticipated within the next ten years, 25% of the experts consider the continuing cultivation and successful differentiation of this cell type generally to be impossible. The assessments of embryonic and adult stem-cell therapies also differ substantially. Overall, the therapeutic application of ESC research bears higher risks, especially for the patients. Table 1 shows the prospects of stem-cell therapies for various diseases, according to the experts we questioned.

The chances of stem-cell therapy being used to reduce tissue impairments caused by cardiovascular, infectious, organic or metabolic diseases, or to reduce the need for organ transplantations, are assessed cautiously. Although these possibilities would be highly welcomed by the experts—their desirability ratings were

Table 1 | Developments in therapy and application

Diseases	Developments in therapy and application
Diabetes mellitus	The use of insulin-producing cells from hASC as well their production from hESC is expected within the next 6–10 years. By contrast, the transplantation of encapsulated xenogenetic islet cells is judged as highly problematic
Coronary heart disease	The treatment of coronary heart disease with autologous hASC is seen as one of the first and most realistic applications of stem-cell therapy. The majority of experts expects this treatment to become widely available within the next 6–10 years
Parkinson's disease	The alleviation of Parkinson's disease by implanting hESC into the brains of patients is also expected within the next 6–10 years. However, 14% of experts doubt that this application will ever be realized
Multiple sclerosis	Multiple sclerosis therapy is not expected within the next 11 years. Clinical trials demonstrating a temporary delay of the disease by implanting glial cells from hESCs are expected in the next 11–15 years. However, 17% of experts do not think that this will ever be accomplished
Paraplegia	The majority of experts also expect the successful use of human stem cells for the regeneration of nerve fibres within the next 11–15 years
Alzheimer's disease	Most experts anticipate the delay or prevention of Alzheimer's disease as a result of stem-cell therapy at the earliest within the next 11–20 years. However, 10% do not expect this to happen at all and another 36% at least not within the next 20 years
Production of complex organs	Experts are very sceptical about the possibility of producing complex organs, such as kidneys, livers or hearts, from stem cells. Almost 90% do not think this can be realized within the next 20 years

significantly high—the majority does not expect their widespread application within the next 20 years. On the other hand, the use of stem cells in toxicology and pharmacology is viewed very optimistically. All the experts anticipate that stem cells will be routinely used in these areas within the next 15 years—almost half of them expect this even within the next five years.

> …there are concrete scientific and medical concerns about the safety of hESCs in therapeutic applications, which further explain the current preference for hASC research in Germany and among German scientists

Other advances based on hESCs, mainly in IVF, germline therapy and cloning, are assessed very sceptically in regard to both their realization and desirability. For instance, only 8.3% of the experts would consider human germline therapy as desirable and more than 80% cannot imagine that it will happen in Germany within the next 20 years. Regarding therapeutic cloning for the production of hESC lines, more than half of the experts also do not expect this within the next 20 years, while one-fifth expects this to never happen in Germany. However, about 60% of the experts expect surplus embryos from IVF to be used as a source of stem cells within the next 10 years, despite the current controversy around this issue.

The possibility that advances in stem-cell therapy will improve the techniques of human reproductive cloning divided the experts: 44% never expect this to happen and another 17% at least not within the next 20 years. However, one-third already anticipates these improvements within the next ten years. In contrast, improvements in animal reproductive cloning are viewed very optimistically. More than 80% expect such advances within the next ten years and 50% within the next five years. But these latter developments would be welcomed by far fewer than half of the experts (14–39%) and they are clearly regarded as risks, especially for patients, but also to a lesser extent for research and industry. Furthermore, societal acceptance and the political and legal framework have a major role in these research areas.

When it came to the question of whether hASCs or hESCs are favourable, the experts are very clear. Within the next ten years, hASC cells will be the most important cell types for research in Germany, according to the study. However, the participants also considered hESCs from the blastocyst, genetically modified hASCs and hESCs, and cells from the umbilical cord, as important. With regards to their potential to differentiate, pluripotent cells will be the most important. When it comes to therapeutic applications, unlimited access is expected for pluripotent bone marrow stem cells, cells from the umbilical cord and tissue-specific hASCs within the next ten years. Moreover, experts are optimistic about the prospects of the standardized use of different hASCs in cell transplantation, tissue engineering and regenerative medicine. In particular, haematopoietic, mesenchymal and epidermal stem cells are expected to be in widespread use by the year 2013.

Our Delphi study also polled experts about the future of the societal, political and legal situation and its influence on stem-cell research in Germany. Here, more than 90% of the experts anticipate that the public debate on the ethical aspects of hESC research will lead to amplified funding of hASC research in Germany. But they do not expect that this will eventually enable Germany to assume a leading position in hASC research and patent applications. Nevertheless, almost two-thirds of the participants expect that, in the next 6–15 years, the majority of the German population will approve of hESC research as a consequence of its medical successes either in other countries or from ASC research. But only one-third of the experts think that this would be a desirable development and one-fifth thinks that a majority acceptance of hESC research will never be attainable in Germany.

Almost 90% of the participants do not believe that an international *de facto* ban on the research and use of hESCs will ever be possible. They also regard such a ban as detrimental to research, industry and patients. In fact, the majority of experts expect the unlimited worldwide import of hESCs within the next 6–15 years. One-third, however, cannot imagine unrestricted import within the next 20 years, or ever. We obtained similar results when asking respondents whether they expect a relaxation of the German Embryo Protection Act, which would allow research on embryos younger than 14 days. In general, this is regarded as an opportunity for research, industry and patients. In contrast, a complete suspension of the Act, which would allow research on embryos even after day 14, is not expected in Germany within the next 20 years (22%), or ever (64%).

The current legal and political situation also bears the risk of a 'brain-drain' of German scientists due to the restrictions imposed on ESC research. Nevertheless, the probability of this is assessed ambivalently: it is either expected within the next five years (47%), or not at all (50%). Another hazardous development might be the increasing commercialization of stem-cell research and therapy. If stem-cell research is predominantly pursued by industry or only aimed at the commercial utilization of therapeutic applications, this is clearly seen as a risk for patients as well as for research itself.

In contrast, the establishment of national or international biobanks to provide researchers with stem-cell lines would be highly welcomed by almost all experts: 59% believe that a German biobank—in cooperation with research institutes and patients—could be established within the next 6–10 years. Within the next ten years, 80% even anticipate an international non-profit stem-cell project to characterize and archive all kinds of embryonic and adult stem cells and serve as a cell-line supply for stem-cell researchers.

There are still various important reasons for the current resistance in Germany to hESC production and research. Ethical concerns, the influence of religious beliefs and the church, and even recollections of the role of medicine in the Third Reich have surely influenced the debate (Knowles, 2004). But the Delphi study conducted with German stem-cell experts reveals that, in addition to these ethical and societal arguments, there are concrete scientific and medical concerns about the safety of hESCs in therapeutic applications, which further explain the current preference for hASC research in Germany and among German scientists.

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