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Ethical Considerations on Stem Cell Research

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1. Introduction

Definitions: First we have to clearly define what we are talking about in the field of stem cells. The zygote (fertilized egg cell) and the cells of the very young embryo up until the eighth-cell stage are totipotent. This expression means that in the appropriate environment (the uterus) these cells can form a complete and normal individual.

In contrast to this notion, the embryonal stem cells of mammals are derived from the inner cell mass of the blastocyst, a slightly later stage of embryonal development. These cells are no longer totipotent, but pluripotent. This means that those cells, if artificially inserted into a heterologous young embryo, survive and give rise to all tissues and cell types in this embryo including cells of the germ line, thus creating a chimeric embryo, which consists of two types of cells that are genetically different from each other. Embryonal stem cells (ES cells) display a few properties that make them highly interesting for regenerative medicine: they can be grown and multiplied indefinitely in the presence of the appropriate “factors” (proteins, growth factors, small molecules) without major genetic changes and without loss of pluripotency, and they can be modified by genetic engineering without major chromosomal changes and without using viral vehicles [1]. The latter property is essential for the future application of those cells for gene therapy. Mammalian ES cell technology was first developed in the mouse model system beginning with the landmark paper of Martin [2]. Human ES cells (hESC) were first isolated by Thomson [3]. The patenting of the isolation of hESC (the so-called WARF patents) led to a huge public discussion regarding the moral and legal implications of those patents [4]. Ultimately the US supreme court acknowledged those patents as being legal, while the Court of Justice of the European Union ruled that no procedures can be patented, which use embryo research, i.e. the destruction of human embryos [81]. However, human in-

duced pluripotent stem cells (hiPSC) can now be created from differentiated adult cells, like dermal fibroblasts (see below), which according to biochemical criteria (transcriptome, proteome), are very near identical to hESC [5]. It has been shown, in the mouse, that not only by biochemical criteria, but also in terms of the developmental potential, mouse iPSC are identical with mouse ESC [6].

In contrast to the pluripotent ES cells, somatic stem cells are multipotent, meaning that their developmental potential is rather limited to a number of related cell types. For instance, the well-known hematopoietic stem cells of the red bone marrow can generate *in vivo* all cells that are found in the blood of humans. Until recently it was believed that this commitment to a number of related developmental fates is absolute, however it is now known that even in normal individuals *in vivo*, a low percentage of bone marrow stem cells can become quite different cells [7], and, to give just one example, fibroblasts can be induced, by expression of two to three transcription factors, to become *bona fide* heart muscle cells [8].

Currently, an ever increasing number of papers on hiPSC (human induced pluripotent stem cells) are being published as documented by indexing services such as PubMed. In vitro methods of creating hiPSC from the easily available dermal fibroblasts were first described in 2006 and 2007 [9, 10]. Due to longer experience with the stem cells of the mouse and due to ethical and legal considerations, there is still a technical gap between procedures applicable to mouse iPSC and hiPSC. Since 2008, a nearly exponential increase in papers dealing with hiPSC is appearing and well over 1000 papers are now being published every year. Many of those papers mention that hiPSCs in contrast to hESCs (human embryonal stem cells) are considered to be ethically acceptable while an intensive debate was and is going on concerning the ethical implications of hESCs [4, 11]; (see below in the next part of this chapter).

Another unsolved problem in stem cell therapy is “homing” of the repaired cells to the “niche” in the body where they are needed and can function. Only in exceptional cases does homing occur automatically (bone marrow stem cells in the mouse), but in other cases (brain) the cells must be directly injected into the relevant area. Modern nanotechnological methods may be helpful for this immense task in the future [12].

What we would like to do in the current paper is (paragraph 2) to give a very short overview of the present and the anticipated future status of hiPSCs and their use in biomedicine including the new topic of differentiated cell plasticity [7]; (paragraph 3) to explain the ethical arguments that were brought forward concerning hESCs; and (paragraph 4) to discuss some remaining ethical arguments concerning hiPSCs with special emphasis on the argument of complicity [13].

2. Short overview of the present and the anticipated future status of hiPSCs

Stem cell and related techniques, such as direct reprogramming of differentiated cells, offer an immense promise for the future of regenerative medicine using stem cell therapy

and/or a combination of stem cell and gene therapy. This promise is, as we now know, a realistic one, but the enormous technical difficulties and the requirements imposed by clinical safety (for instance concerning the cancer risk) are not easily overcome and we estimate that many years will pass before these methods become clinical routine for many diseases. Presently, very few clinical examples exist that successfully show the efficacy of stem cell and gene therapy [14].

The theoretical and biological basis for the techniques to be discussed here are, among others, the fact that somatic cells of animals (and of the human animal, of course) contain the same genetic complement as the fertilized egg cell (the zygote). This means that every gene needed for the complete development of an individual is present in every somatic cell of a mature individual. The direct and undisputable proof for this is shown by the cloning of animals [15]. However a similar result was obtained decades before “Dolly the sheep” by John Gurdon [16], working with frogs. Therefore, the phenotypic differences between different somatic cells of an adult individual must depend on differences in gene expression, or to use a modern term on the “epigenome” of those cells. At present Bio-medicine is, at an increasing speed, discovering methods to change this differentiated state from one well defined cell type (say fibroblasts) to another (say, for example, a specific subtype of neurons needed for an individual patient) [7]. Previously, the differentiated state of somatic cells was believed to be immutable, at least *in vivo*, but this paradigm clearly is no longer true. Why are such procedures needed in regenerative medicine? This question leads us to the genetic differences between human individuals and the immunological incompatibility between humans who are not monozygotic twins. For reasons that are not entirely clear to scientists who study the evolutionary history of mankind, it appears that differences in the antigens of the HLA type (human lymphocyte antigen; displayed on cell surfaces) occur between any two humans and are large enough to lead to immunological attack (host versus graft disease) after the transplantation of cells and organs. Therefore, it is desirable to use autologous (HLA-compatible) cells for therapy, which raise no immune response and make immune suppression of the patient superfluous. In organ transplantation, this problem is generally overcome (although, perhaps, insufficiently) by the pharmacological immune suppression of the patient who receives a transplant. For the combination of gene and cell therapy, the idea is to use autologous cells which, however, must conform to strict safety standards before a clinical trial is granted by the authorities and can be started. There are also a number of unresolved problems if the autologous cells to be transplanted need a genetic “repair” because the patient to be treated suffers from a genetic disease whose underlying mutation is known and will be corrected by sophisticated genetic engineering as is applicable to human cells.

Genome editing: For several reasons which have to do with differences that exist between mouse and human iPSCs, as well as with the low success rate of current methods for genome editing [17], the originally developed ingenious method of selection and counter-selection in mouse ESCs [1] seems not to be suitable for a safe repair of known mutations in genes of a patient suffering from a particular and genetically well-known inherited disease. Ideally, the presence of the mutation in question should be known by DNA sequencing of the relevant part (or the whole genome) of the patient. Instead, the scientific community is

now seeking to improve the efficiency of point-directed genome editing to clinically acceptable levels [17]. The cells to be used for these procedures should be as close as possible to the original patient-derived cells, avoiding prolonged proliferation of hiPSCs. The tools that must be developed to achieve this are the so-called ZNF-nucleases (zinc finger nucleases) based on a concept by Kim [18] which can produce a double strand break at a precisely defined point in the whole human genome [17]. This double strand break is then recombinogenic enough to lead to homologous recombination with a co-transformed plasmid that carries the corrected DNA sequence [19]. Alternatively, the TALEN strategy can be used [20]. One problem that must be overcome here in the future, is the limited capacity for proliferation of differentiated cells and their general reluctance to be transformed by plasmids, which is true for instance for dermal fibroblasts.

Cancer risk: One of the greatest obstacles that must be overcome before stem cell therapy can become clinical routine is the inherent cancer risk conferred by both ESCs and iPSCs. In one of the very few and frequently-quoted clinical trials for gene therapy of X-SCID, some of the affected and essentially cured children came down with leukemia. The reason for the cancer incidence in this case was the lack of control of the point of integration of the viral vector used to introduce the genetically corrected gene sequence, which was inserted at locations in the genome where it caused leukemia [21, 22]. However, even ESCs or iPSCs which are not genetically manipulated, by their “stemness” alone can cause cancer. It must not be forgotten that embryonal stem cells were first discovered during the study of teratocarcinomas and one of the most important decisive traits was the ability to form teratocarcinomas in nude mice [2]. Therefore, for some time, the idea was to re-differentiate the hiPSCs to the needed cells after genetic manipulation and then purify these cells until they were essentially free of remaining stem cells [23]. This proved to be a difficult job. The other solution to this problem is to directly produce the desired cell type using the action of transcription factors and small molecule signalling substances without ever going through a stage of stem cells [7]. This way is very promising but also not yet matured enough for clinical practice.

In summary, we may say that it is still too early to decide in which direction future cell and gene therapy will go. For some time, hESCs, and even more importantly, hiPSCs will be needed for biomedical research. This is not restricted to gene therapy and cell therapy without genetic corrections (as in the case of acquired diseases), but equally is needed for the establishment of disease models and for drug testing, which is, however, not the topic of this chapter. For all of those reasons, we think it is timely to discuss the ethical implications of stem cell research.

3. Ethical arguments brought forward concerning hESCs

The central ethical concern that is raised by production and use of hESC is the question concerning the moral status of human embryos. The derivation of hESCs from early embryos (blastocysts) is, in practice, necessarily connected with their destruction. Because of that, we

have to ask, if a human embryo is recognized as a being endowed with human dignity and a right to life comparable to that of born human beings. Destruction for research purposes raises the serious ethical issues of exploitation, instrumentalisation and killing of human beings. Concerning both ethical issues, human dignity and the prohibition of killing, in regards to human embryos in spite of the long discussions an ethical consensus is nowhere in sight. In the following passage some explanations will be given regarding the fundamental question of the moral status of embryos [12, 24-31].

Further intensively discussed issues in hESC research are research cloning (the procurement of embryos for research purposes by nuclear transfer in enucleated egg cells) and the donation of egg-cells. For a long time, the development of therapeutic applications seemed to involve research cloning (also called "therapeutic cloning"). Research cloning of humans would represent a clear instance of exploiting humans solely for the benefit and interests of others. Establishing this technique in humans requires further destructive embryo research and is feared to prepare a slippery slope for reproductive cloning of humans, which is generally considered as ethically unacceptable [32-37].

If this way to therapeutic applications had succeeded, the demand for a high number of donated egg-cells would have been a consequence. For women, egg donation causes health risks and the danger of commercial exploitation. The alternative to produce hybrids of humans and animals is also seen as offending human dignity [38]. These ethical problems have lost some urgency, since this strategy doesn't seem to be succeeding. The fundamental question of the moral status of human embryos is still a matter of open discussion in ethics.

3.1. The discussion about the moral status of early human embryos

hESCs needed for research are obtained from different sources that entail a different ethical evaluation. While extraction of stem cells from adults, from umbilical cord blood or from aborted foetuses, is considered to be ethically acceptable under certain conditions, the procurement of hESCs is confronted with ethical objections, since it is necessarily connected with the destruction of human embryos. It is a kind of consuming embryo research. The possible sources are already established embryonic stem cell lines, supernumerary embryos from IVF-treatment, embryos produced specifically for research purposes or even embryos cloned by nuclear transfer as a logical consequence in case of successful therapeutic applications.

Different regulations worldwide and in the EU, as well as an on-going discussion about the funding of research projects are taking place [12, 39]. As a minimal consensus, creation of embryos solely for research purposes is forbidden in the European Council's Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine [32].

By obtaining hESCs from the inner cell mass of a blastocyst for research purposes beginning human life is destroyed. The embryo is obviously a human being, a member of the human species, has an individual genome, neither identical with that of the mother nor that of the father, in contrast to other human tissue, can develop into the full shape of a

human being (totipotent) and has a small, but realistic chance to be born and live its own life.

Since hESC research, on the one hand, gives hope in terms of therapeutic applications for severe diseases and, on the other hand, is connected with the destruction of embryos as necessary means to this end, two ethically high standing aims are opposed. Basic research (freedom of research) and the hopes connected with therapeutic application (principle of beneficence, value of health and life of patients) are confronted with the respect for human dignity and the right to life of human embryos. The question is: May human embryos be produced and destroyed as biological material for research and therapy or even for industrial applications?

In relation to already born humans we would never accept such destruction or killing no matter how great the benefit for research or therapy could be. For born humans there is a strong agreement: They have moral status and equal human dignity independent of their actual abilities or disabilities. The statement about the moral status is a value judgement. At first it means that humans have intrinsic value. If the moral status of humans is determined in the tradition of the German philosopher, Immanuel Kant, with the term "dignity", an unconditional value is proclaimed, which goes beyond the intrinsic value of non-human beings and can't be balanced with the benefit of others. Kant makes this clear in a well-known quote regarding his categorical imperative: "Act in such a way that you treat humanity, whether in your own person or in the person of any other, never merely as a means to an end, but always at the same time as an end." [40, 41].

The central consequences of the recognition of equal human dignity are the fundamental equality of all humans with regard to this dignity, the same right to welfare and the prohibition of arbitrary instrumentalisation and exploitation for the purposes of others. Killing for research purposes definitely falls under this prohibition. Whether and to which degree these moral demands are already valid in the early stages of development, is a matter of the controversy concerning the ontological, moral, and legal status of human embryos [36, 42-47].

It is therefore clear why this discussion is unavoidable. Before discussing freedom of research, hopes for therapeutic applications, and different possibilities of regulations, the question, of whether or not embryos, in an ethical respect, belong to the community of beings deserving equal and impartial consideration, must be answered. Is impartiality (the "golden rule"), to be applied even to embryos, or not at all, or merely in a gradually weaker sense?

These issues were discussed extensively in the last decades and, regrettably, have not achieved a consensus. Here we will shortly explain the general lines of reasoning. Summarized in a simplified overview there are three types of answers: (a) Personalistic positions maintain human dignity and a right to life of human embryos. (b) Non-personalistic positions deny that and impute to embryos a status similar to human tissues or cadavers. A third group proposes to find a kind of middle position by giving several types of (c) relative or gradualistic answers.

- a. **Personalistic positions** claim that already the embryo must be respected as a person and, therefore, has a right to life in the earliest stage and also outside the mother [42, 48-52].

The reason for personal positions is a certain view of the embryonic development. The development from fertilization up to birth is understood as a continuous development (*argument of continuity*) of something that is, basically, already present, and under natural conditions, has the inner capability of further development into a fully evolved person (*argument of potentiality*) and remains the same being (*argument of identity*). The embryo is not a preliminary stage of a human but a human in the earliest stage. Although it doesn't have the actual abilities of a person (self-consciousness, reason, freedom), the embryo must be treated as a person because of its inner potential to develop these qualities and, under normal circumstances, become such a person.

This reasoning can be combined with two additional arguments. The *species argument* points out that the embryo's membership in the human species is a biological fact. Biological facts alone are not sufficient reasonings for moral judgement. However, the argument may serve as a determination of the scope, the application area of dignity: All members of the human species are included. Being a member of the human species and being endowed with dignity and certain rights is actually coinciding with each other. Therefore, the species-membership suffices to claim the corresponding rights. If this argument also applies to embryos, then this is controversial and presupposes the first three arguments. The four previously mentioned arguments are often described as a "SKIP-quadrology": species, continuity, identity, potentiality [44].

Sometimes another argument is added in respect to the remaining uncertainties of empirical knowledge, as well as philosophical interpretation of early embryonic development. The *precautionary principle* generally calls for a careful proceeding in small steps and imposes the burden of proof on those, who want to change existing attitudes and moral norms. They have to offer evidence, not those who defend them. According to this position, doubts about being a person may not lead to an arbitrary restriction of human dignity. No man is subject to the constraint of having to justify his existence. This corresponds to the basic structure of the human dignity argument, which should, primarily, serve as protection of the weak against any kind of discrimination. Everyone is basically interested in safe conditions, in which she/he need not fear being excluded from the common protection area due to some actual lack of abilities or characteristics [45, 53].

The consequences of the personal position are unambiguous: Destroying embryos for research purposes and research cloning is forbidden. Freedom of research is subjected to moral limits. Therapies, which cost the lives of other humans, are not acceptable. Even the hope for therapy for serious diseases is no adequate reason for the specific production and destruction of human embryos. Nevertheless, each mentioned argument is subjected to criticism and the personal position hasn't turned out to provide a consensus [42, 43].

- b. **Non-personalistic positions** deny what personalistic positions proclaim.

A far-reaching objection to the personal position is, for example, represented by the Australian moral philosopher, Peter Singer. He denies the human dignity of embryos, fetuses and even newborn children due to a very narrow concept of personality based solely on actual abilities: "My suggestion, then, is that we accord the life of a fetus no greater value than the life of a nonhuman animal at a similar level of rationality, self-consciousness, awareness, capacity to feel, etc. Since no fetus is a person, no fetus has the same claim to life as a person." [54]. For these positions there is, in principle, no objection to hESC research as long as the rights of the donors of gametes or embryos are respected.

- c. **Gradualistic positions** try to find a way of maintaining special respect for human embryos and restrictions of research purposes and, at the same time, allowing research for high standing objectives. They are quite frequently supported [29, 31, 55-58].

According to this kind of reasoning full protection of human embryos starts at a later stage of development. The time before the moral status is gradually weakened, but not reduced to that of some other human tissue. Most frequently nidation, or the end of the possibility of twin formation, is seen as the relevant moment. When nidation is complete, the embryos' chance of survival increases significantly. Sometimes other stages of development are argued as being relevant e.g. the beginning of the first nerve cells in the fifth or sixth week. This is seen as relevant, if the ability to feel pain is seen as a decisive ethical quality.

Finally, there are suggestions in which the moral status of embryos isn't differentiated depending on the stage of development, but according to the context and target of its creation. In such an "extrinsic" determination of the moral status surplus embryos from IVF-treatment and research embryos don't have any dignity, because they lack the necessary conditions for further development, or according to their creators' intentions, never should be born at all, while embryos produced for IVF-treatment already have this dignity in a very early stage, since the intention and hope is that they be born [24, 59, 60]. In this way of reasoning, dignity and the right to life are conferred or awarded by society. Dignity depends on the allocation to the research department or the IVF department. Some authors turn this reasoning into the field of metaethics and proclaim, that human dignity is always invented and awarded by society and not based on an objective moral reality [58].

If the protection of some early stage or research embryos or surplus embryos is weakened, the interests and well-being of embryos and patients can be balanced against each other and destruction of embryos can be justified for high standing objectives. Strict embryo protection is argued to be valid for later stages and a clear limit seems possible for the time being. Nevertheless this reasoning is not free of some arbitrariness and, if the restrictions are sustained, one can fear for the time, when interests for research with later stages of embryonic development will emerge. In principle, everything seems justifiable, if dignity depends on society or the intentions of the embryo's creators.

Some authors try to justify hESC research without weakening the moral status of embryos through a special reasoning within the prohibition of killing [61, 62]. In an opinion of the

Austrian Bioethics Commission these attempts are summarized as follows: “The first argument chooses the comparison with the removal of organs from brain dead patients. This does not violate the prohibition of killing nor the prohibition of the complete instrumentalisation of a human life that is derived from the concept of human dignity. Even less should the use of fertilised egg cells at a stage in which one cannot speak of either an organ or brain development be rejected as such on ethical reasons. The second argument compares the obtaining of embryonic stem cells from surplus embryos with the medical use of tissue from aborted fetuses, which can be ethically justified in so far as the abortion was not performed for the purpose of obtaining foetal tissue. Both lines of argument imply that at the moment it is no longer used for reproduction, the embryo created in vitro undergoes a change of status that is equivalent to that of a person's transition from life into death. Even if one wishes to accord the fertilised egg cell personhood, this does not mean that there is an irresolvable conflict of values between the protection of life for the embryo and the freedom of research in the service of present and future patients”[31]. These arguments cannot be discussed here [63, 64]. The intention to escape the endless discussion about the moral status of embryos is clever, the hope to prevent the weakening of the human dignity argument may be honourable, but as a matter of fact, the relevant embryos are not dead prior to the destruction for research. One might wonder, what results this kind of reasoning could have, when applied to disabled persons or patients at the end of life, which could also be said to have no chance for further development (a logical version of the slippery slope-argument).

3.2. Results of the status debate

Each modification of ethical reasoning and central moral attitudes must be paid attention to in terms of consistency, rationality and possible side effects for other areas of life. This examination of the arguments is sometimes more important than the solution itself. Bad arguments are counterproductive, promote distrust against ethical reasoning and science in the long run, and weaken their aptitude to give orientation. The first task of ethics is the effort to obtain good reasons, not fast answers [65]. The personalistic positions are consistent in the protection of the right to life, but have trouble convincing society and researchers. The non-personalistic positions will not find approval because of the openly declared consequences for new-born children, disabled, or dying persons. The middle positions try to release research from some ethical borders, without damaging the conviction of equal human dignity. But their methods of reasoning don't really convince and, in the long run, leave open too many options.

Nevertheless two fundamental considerations seem to support maintaining a rejection of the destruction of human embryos for research purposes:

- a. If someone wants to justify hESC research, either within a limited extent or up to research cloning, she/he must be able to give convincing arguments, why embryos might be treated in a different way than born humans. This seems to be impossible without weakening or denying the moral status of early human embryos. This method of reasoning possesses danger of weakening the protection of the human dignity in general. If the coincidence of human species and human dignity is given up and exchanged for a

dignity awarded by society, corresponding to actual research interests, serious doubts may arise, whether the desired protection standard can be maintained in other areas of life, e.g. for coma patients, disabled people or new born children.

- b. hESC research including destruction of human embryos is not without alternatives. The promised therapeutic applications of hESC research are still lacking, while research in adult stem cells and hiPSC research seem very promising and are reducing the ethical objections. When opposition to hESC research is still accused of impeding research and preventing necessary new therapies, this could also be seen as a clever policy of small steps to deceive moral convictions. Also other objectives are highly relevant, for example industrial applications in toxicity testing with human embryos as a substitute for animal experiments: "These cell lines may provide more clinically relevant biological systems than animal models for drug testing and are therefore expected to contribute to the development of safer and more effective drugs for human diseases and ultimately to reduce the use of animals. They also offer the possibility to develop better in vitro models to enhance the hazard identification of chemicals. It is possible that these applications will turn out to be the major medical impact of human ES cell research..." [66].

4. Remaining ethical arguments concerning hiPSCs with special emphasis on the argument of complicity in another's wrongdoing and double effect reasoning

If it is true that successful therapeutic applications are more likely to result from hiPSC research than from hESC research, ethical problems would be reduced significantly [4, 26, 67, 68]. Research cloning could be avoided. It would never be necessary for therapeutic application. hESC-research would, at least, be reduced to the domain of basic research and control experiments. For this remaining need it seems realistic that already existing cell-lines will be sufficient [12]. In this case, the destruction of human embryos for research is completely avoidable in the future and even the destruction of surplus human embryos may be unnecessary.

Nevertheless, even in hiPSC-research, some ethical issues remain and are in need of intensive consideration:

Can the distinction between hESC and hiPSC be explained in a consistent and convincing way? Is it possible to find a reliable delimitation between pluripotent and totipotent stem cells? Is it possible to prevent the production of germ cells out of hiPSCs, as well as their use to create new research-embryos [26]?

Is the assumption that hESC-research is completely dispensable, or will be after a period of time, justified, or is it only a means of sedating the conscience? Some scientist say, that is too early to decide [11]. Even a temporal limited "exception", or a limited number cannot be seen as an exception of ethical principles but must be justified. If further destruction of a limited number of human embryos for research purposes would be necessary during a transition

period, some ethicists argue for the use of surplus embryos from IVF-treatment [31]. The ethical objections were indicated above. This way is surely not acceptable, if, according to our appraisal, existing cell lines are sufficient. If not, the use of surplus embryos needs to be justified in a consistent way without denying the human dignity of embryos and without opening the way to the creation of research embryos on demand and even for non-therapeutic applications.

How can the cell donors' right to voluntary and informed consent, as well as the protection of personal data, especially in the case of application of hiPSCs as disease models, be guaranteed? How can the relevant questions of property rights and patent law be solved [69]?

Even hiPSC-research is, in several ways, confronted with the ethical problem of "complicity in others' wrongdoing": How can someone consistently reject the destruction of human embryos and, at the same time, use the result of former destructive research [13, 47, 70, 71]? Katrien Devolder draws attention to this problem of complicity. She contradicts the opinion, that hiPSC research is ethically correct, while hESC research is wrong because it involves destruction of human embryos: "Many who object to human embryonic stem cell (hESC) research because they believe it involves complicity in embryo destruction have welcomed induced pluripotent stem cell (iPSC) research as an ethical alternative. This opinion article aims to show that complicity arguments against hESC research are *prima facie* inconsistent with accepting iPSC research as it is currently done." [13].

In this passage we would like to scrutinize her theses and her suggestions for a solution. We are convinced that the problem of complicity is no obstacle for hiPSC research, if certain requirements are met.

4.1. Double effect reasoning

In theological and philosophical ethics, problems like this (cooperation with another's sin, "cooperatio in malo") can be discussed in relation to the so-called "principle of an action with double effect", in brief "principle of double effect", or "double-effect reasoning" [72-74]. In this principle, a distinction is drawn between direct consequences of an action and side effects, which are only indirectly wanted or accepted as unavoidable. The principle wasn't interpreted and used uniformly and has undergone some changes. In philosophical and theological ethics, it is relevant in two different contexts. The first and original context is the question of cooperating with the sin of another person. In these cases, the wrongness of the action is presupposed and the question concerns only the legitimacy, or culpability of the cooperation. Furthermore the principle of double effect is relevant in the context of some specific moral norms, such as the prohibition of killing to determine moral rightness or wrongness. In these cases it is a principle of restrictive interpretation of deontological moral norms [75]. This is an issue of high complexity and not necessary for the question of complicity. In the first context, the principle draws one's attention to several relevant aspects that may be helpful for our question of complicity in hESC and hiPSC research.

The basis of the argument of complicity with another's wrongdoing is the estimation that somebody, who cooperates in, or profits from the morally reprehensible actions of other

persons, makes himself responsible in a certain way as an accomplice. "Complicity" means a culpable cooperation in the ethically wrong action of another person. The conviction that we are responsible not only for the immediate results of our behaviour, but also for the influence we exert by our behaviour on convictions and behaviour of others in the long run, as far as this is foreseeable, is fundamental.

Just as the demands of morality are aimed at the inner attitude as well as the outer actions of man, accusations of complicity are not only aimed at a voluntary and deliberate cooperation in the wrong actions of others, but also at inadequate attitudes towards the wrong actions of others. Our inner disposition, our fundamental attitude, our character is the central content of our moral obligation. Morality primarily consists in the fundamental attitude of impartial benevolence, in the respect for the equal dignity of all humans. Motives cannot be recognized directly but only inferred from our behaviour. Sometimes adequate symbolic actions can help to express the inner attitudes and prevent misunderstandings. Symbolic actions partly get credibility by the costs they cause and by the disadvantages somebody is ready to accept [76].

This effort especially is necessary if somebody profits from the wrong actions of others and thus, gives the impression of approval or inner consent of these actions. This can even be the case, if one wasn't involved in the wrong actions at all. The use of research results from morally reprehensible experiments in the past [77] without an explicit dissociation can give the impression of lacking sensibility and missing respect for the victims or even the impression of an inner consent, of condoning or justifying these actions. If there are scientific reasons to use the results, the rejection of these crimes must be articulated by explicitly remembering the victims and condemning the crimes.

Complicity with another's wrongdoing can happen in different constellations. In the tradition of moral theology, different types of cooperation with the sin of another one were distinguished and relevant distinctions were made for the degree of guilt [74, 78, 79].

In any case, the rejection of a sin, a willingly performed wrong action of another person, is required. Complicity, as an inner consent when another one's sin "is wanted as such", is called "*formal*" cooperation and is always wrong. Even an implicit inner consent is seen as a formal cooperation, especially in the case of serious offenses. If the inner consent is missing because the cooperation happens involuntarily or without knowledge, this is called a "*material*" cooperation. However, this kind of cooperation requires a justification, but, in contrast to a formal cooperation, this is possible. According to traditional arguments a material cooperation is permitted, if the other's sin is "wanted only indirectly" and the action corresponds to the rules of the "principle of double effect".

Within the principle of double effect, a distinction is drawn between direct consequences of an action and side effects, which are only indirectly wanted, or accepted as unavoidable. While direct cooperation is regarded as forbidden, the indirect one can be justified by adequately important, so-called *proportionate reasons* for accepting the others' sin. In this way, teleological reasoning, on the basis of balancing good and bad consequences, is made possible for the indirect causation of the others' sin. Nevertheless, this remains excluded for a di-

rect causation or a direct intention, in which the wrong action is intended itself (*per se*), or as a means to an end [80]. In these cases the sin must be seen as directly intended. As a minimum for speaking of an indirect causation of an evil, it was demanded that good and bad consequences must result from the action "at least equal immediately" [73, 74, 78].

In casuistry, further types of a "material" cooperation were distinguished: A *positive* cooperation by an active action is more serious than a *negative* cooperation by omission of an action. An *immediate* cooperation is more serious than a *mediate*. A *near* cooperation is more serious than a *remote* one. Necessary cooperation, without which the wrong action of another one wouldn't have happened at all, is worse than cooperation, when it would have been performed anyway. A direct intention could be suspected, the more immediate and more near one's own action is connected with another one's sin and the more probably the other one wouldn't sin without this cooperation. Here the principle includes a difficult question: Does the indirectness and justifiability of complicity primarily depend on the causal proximity, or on the probability of another person's wrong action? Is it really less problematic to promote a wrong action with high probability, if the number of mediating instances is increased? In the theological tradition there was no agreement on this matter. According to a teleological method, responsibility refers to all foreseeable consequences that can be influenced by one's actions. In this point of view, probability is more important than proximity. For the credibility of the inner consent, proximity may be the greater problem.

These distinctions show the difficulties in dissociating oneself consistently from another's wrongdoing while cooperating or profiting from it. While the distinction between formal and material cooperation is a clear alternative, the distinctions of types of material cooperation seems in real life often to be a matter of degree. At least one could say, that the effort to make one's own inner rejection of another's wrongdoing credible to other people is greater, the more a cooperation is near, immediately and necessarily.

The principle of double effect includes at least three relevant aspects that may help to evaluate the problem of complicity in hESC and iPSC research: (a) In any case, the rejection of another one's action, which one determines as ethically wrong, is required as matter of inner consistency. (b) A material cooperation can, nevertheless, be ethically justified, if intention and causal relation can be seen as indirect, which is sometimes clearly identifiable, but is often a matter of degree. (c) In any case, a proportionate reason for accepting the others' sin must be given. Additionally sometimes symbolic actions will be necessary to maintain one's credibility.

4.2. Complicity according to Devolder

Devolder's statements to complicity partly correspond with these arguments. She introduces the following variants [13]:

1. "Causally contributing": "When I induce or encourage you, or provide you with the means to commit a murder, and as a result you commit it, I am complicit in that murder." In these cases, the other's wrong action is also the result of one's own action.

2. "Promoting wrongdoing through increasing demand for embryonic stem cell lines": "One can be complicit in wrongdoing by increasing the likelihood of that wrongdoing (or future instances of it) in certain ways, even if one does not in fact cause it."
3. "Promoting wrongdoing through altering attitudes to embryo destruction": Further ways of promoting wrongdoing "include condoning a wrong or fostering more permissive social attitudes towards it." Profiting from the use of the results of a wrong action can awake the assumption that one excuses this action. This can in the long run weaken social attitudes and promote wrong behaviour.
4. "Implicitly condoning wrongdoing and disrespecting its victims": Complicity can also be supposed, independent of the consequences, if an implicit excuse of a wrong action, or disrespect towards the victims seems to be expressed.

In the terminology of theological ethics, paradigms 1-3 refer to different forms of material cooperation. The first includes examples of direct and indirect cooperation specified as near forms of cooperation. Category 2 and 3 are examples of mediate cooperation of a more remote type, the acceptance of a wrong action as a side effect. One's own action is not sufficient for the realization of this side effect, but increases its probability in connection with others. In contrast to Devolder, this can also be seen as a kind of causation, but an indirect one. In Example 3, the side effect is a problematic change of social attitudes. This effect is even more remote. The connection is a very complex one. It is unquestionable that research often changes social attitudes. Researchers should think about such consequences, which occur as a result of their work. But they aren't alone responsible for it and their actions are seldom a sufficient condition for a change of social attitudes. Category 4 refers to the appearance of an inner consent, which is called an implicit formal cooperation. Either the actual inner attitude or the publicly noticeable expression is not adequate.

4.2.1. Devolder's criticism of hESC research

According to Devolder hESC research is confronted with the problem of complicity even if researchers use already existing cell lines and don't themselves destroy human embryos. Even if there is no direct causal contribution, they contribute to an "increasing demand for embryonic cell lines" [13, p 2176] and, in this way, promote the likelihood of "further embryo destruction" [13, p 2176]. At least at a collective level, this mediate and remote effect is a reality. Presupposition for this criticism is that destroying human embryos is determined as ethically not justified.

A strategy to prevent this contribution is "separating the use of hESCs from their derivation by instituting a cut-off date" [13, p 2176]. This method was used by the jurisdiction in Germany when trying to deal with the problem in 2002. When the cut-off date was moved in 2007, the credibility of the proclaimed objection to the destruction of embryos was damaged. If the shift of a cut-off date can be anticipated, contribution to an increasing demand is not prevented any more. Devolder emphasizes, that even when using hESCs produced before a cut-off date successful research may promote the destruction of embryos in less restrictive countries. As a counter-argument, she points out that hESC lines are mostly derived from

discarded IVF embryos. Since they are available in a large number, hESC research will not increase the likelihood of embryo-destruction in any way. Of course this objection presupposes the acceptability of the destruction of surplus IVF embryos, which is an open discussion. In addition to this, the question arises, of whether or not research interests truly have no effect on the production of surplus IVF embryos [71].

Furthermore, Devolder indicates complicity by contributing to altering attitudes in society, changing moral beliefs, legislation or incentives. In this way, the potential benefits of hESC research for many people and the good reputation of biomedical research in general may weaken efforts to reduce the number of embryos discarded in IVF.

Finally, hESC research is accused of “implicitly condoning wrongdoing and disrespecting its victims”. If the destruction of embryos is evaluated as a kind of wrongdoing, it is inconsistent and not credible, when researchers, who benefit from it, would regret or try to distance themselves from the practice of destruction of embryos. By using the stem cell lines, they seem to condone the way, they were obtained.

4.2.2. Devolder's Criticism of hiPSC research

hiPSC research enables the development of illness specific or patient specific pluripotent stem cells without supply of oocytes and without the creation and destruction of embryos. Thus, the central ethical objections seem to be removed. Contrary to widespread opinion, Devolders thesis is that, regarding complicity with the destruction of human embryos, hiPSC research is in a similar situation as hESC research. hiPSC research wouldn't be a solution for the ethical problems connected to hESC research. She “aims to show that complicity arguments against hESC research are *prima facie* inconsistent with accepting iPSC research as it is currently done.” [13]. She suggests that, in a consistent way, both should be accepted or rejected.

Devolder accuses hiPSC research of „promoting and condoning embryonic stem cell research“. The connections between hiPSC and hESC research seem to be similar to the connections between hESC research and embryo destruction: “Research on hESCs arguably promotes embryo destruction through increasing demand; similarly iPSC research arguably promotes hESC research in the same way. Engaging in hESC research arguably also implicitly condones embryo destruction, in part because it involves significant interaction with those who destroy embryos. Engaging in iPSC research involves even more significant interaction with hESC researchers and thus, even more plausibly, implicitly condones hESC research.... Consistency requires that considerations of complicity are invoked in both cases.” [13]. To a great extent, hiPSC research uses results of hESC research and therefore cannot dissociate itself in a credible way from it. It seems to be contributing at least implicitly to weakening the rejection of the destruction of embryos. If hESC research is opposed because of complicity, according to Devolder, even hiPSC research must be seen as highly problematic, unless several modifications are implemented [13].

4.3. Application of double effect reasoning

The argument of complicity legitimately asks for justification of the involvement of hESC research and in a more remote way hiPSC research in the destruction of human embryos, even if researchers don't perform it themselves. Double effect reasoning can give some general guidance for performing research with including benefits from objected research in the past and unintended side-effects in the future. Researchers must look back and consider, how they think about the way cell lines, were obtained via the destruction of human embryos in the past. Their research should be in consistency with this judgement. They should also think about their contribution to further destruction of human embryos in the future. They should pay attention to the way their research changes the attitudes of society. Both kinds of consequences are part of the responsibility of researches to the extent they can be foreseen as being in some direct or indirect, close or remote way connected to their scientific work.

The possible indirect and more remote consequences of hiPSC research on the destruction of embryos cannot be denied. Who opposes the destruction of embryos for ethical reasons and nevertheless participates in hiPSC research, can be justified in the line of double effect reasoning only, if the rejection of the destruction of embryos and of possible problematic research in other countries is honest and proven by the attempt to minimize the effect of one's own research on promoting further embryo destruction. This objection should also be made public in some clear and unambiguous way and should be accompanied by institutional or legal precautions to avoid further embryo destruction and weakening of social attitudes. The remaining indirect or remote contributing can be justified, if the benefit of the research is adequately high.

4.4. Consistent solutions?

Devolder suggests 5 possible solutions [13]:

1. Rejection of hESC research, as well as hiPSC research.
2. Radical separation of the two research areas and "a change in the ways iPSC research is done so that it would no longer involve complicity in hESC research."
3. One could argue that hiPSC research is considerably more remote from the destruction of human embryos and is, in this respect, less contributing to a weakening of the social sensibility for the victims. In this respect, the "moral costs" could be justified more easily.
4. Complicity arguments could be rejected or limited to cases "when one actually and significantly causally contributes to more embryo deaths", which is not the case for research with stem cells obtained by others.
5. The wrongness of the destruction of human embryos for important research areas could be denied. In this case, the discussed complicity arguments would no longer be pertinent to both ways of research.

Rejection or radical separation of the two research areas are regarded as unappealing by Devolder, because this would be connected with considerable disadvantages for research. A complete renunciation would retard important research projects and be a disadvantage for potential patients hoping for new therapies. The renunciation would be a credible sign, but a burden for others is a problematic proof of one's own integrity.

A possible solution might be seen in a combination of Devolder's suggestions 2 and 3. The change in the ways hiPSC research is performed could be a radical constraint on the already existing stem cell lines and a credible renunciation of obtaining new stem cell lines, or using new ones from other countries, such as e.g. the European Group on Ethics proposes in its opinion 22: "The derivation of new toti-potent cells or pluri-potent stem cell lines from donated pre-implantation human embryos or embryonic cells, or via nuclear reprogramming, is not funded by the EU Research Programme." [12]. If existing cell lines are sufficient for the necessary comparison studies, research for therapeutic applications will not be hampered or retarded any way and no direct or near contribution to further destruction of embryos is remaining. If applicable regulations were found on a broad basis, protected in a credible way and maintained in the long run, complicity arguments pertaining to embryo destruction in the future wouldn't be applicable anymore to hiPSC research. If, according to the latest reports, the stage of pluripotency were dispensable for therapeutic applications and adult stem cells could be developed into desired cell types without this step [7], even the control studies with hESCs would become less important.

An important step in the direction of a limitation of research to existing hESC lines is the European registry of existing hESC lines: "The European Commission has therefore decided to establish and fund a European registry for human embryonic stem cell lines in order to help researchers to optimise the hESC resources available, avoid duplication of work and/or the creation of new cell lines where possible." [12]. This kind of policy helps to avoid the new destruction of embryos and enables transparency and credibility. Regulated in such a way hiPSC has a good chance, not to contribute to a weakening of the social sensibility for the victims of research and to changing attitudes to the dignity of human embryos. More likely it is a step towards the opposite direction of more respect for human dignity.

Devolder's suggestion 3 and 4 refer to the distinction of causally direct and indirect action. The argument, "that the complicity arguments for rejecting hESC research are stronger than the complicity arguments for rejecting iPSC research" [13] seems appropriate to us. Conforming to the principle of double effect, the distinction between immediate consequences and side effects, which are only wanted or accepted indirectly, opens a way to justify these kind of consequences by proportionate reasons like the high benefit of research for fighting diseases in the future. The remaining indirect and remote contribution to the destruction of embryos can be estimated as balanced as long as it is not actively supported and possible usage of results out of this kind of rejected research is not secretly hoped for.

Of course clarification is needed, which research objectives are regarded as adequately high for the use of hESC lines. Therapeutical applications for humans can be regarded as adequate, also necessary control experiments for research with adult stem cells or hiPSCs. But serious doubts appear in relation to non-therapeutic industrial applications like toxicity test-

ing to replace or reduce animal experimentation. Here the opinions are divided and depending on the ethical background, using hESCs for applications like these are seen as a welcome improvement by the one side [12, 66], or as a disproportionate means and a way of damaging human dignity that is not acceptable by the other side. The European Group on Ethics stated clearly: "Although the Group is aware of the importance of respecting animal welfare, it is concerned that respect for human dignity may not be maintained when hESCs are used in toxicity testing of industrial or other commercially produced chemicals not related to drugs, such as cosmetics, or for replacement of animal testing. Therefore, particular attention is to be drawn to this issue." [12, 38, 69, 81]. The demand for further destruction of embryos would be increasing enormously and one can suppose that social attitudes would really change in the long run, if cell lines derived from human embryos are used as commodity, as raw material in industrial dimensions.

Devolder's fourth solution, narrowing "complicity" to cases "when one actually and significantly causally contributes to more embryo deaths" [13], is no convenient way. It tends to reduce researchers' responsibility too much. Mediate and remote consequences of research are part of the researchers' moral responsibility. Abuse of discoveries and inventions, the promotion of personally rejected methods and applications and even a problematic modification of social attitudes are relevant objects of responsibility, as far as they can be foreseen and are enabled or promoted by one's own activity. Taking responsibility of course doesn't mean being accused for every effect, but being willing to give a justification for accepting unwanted side effects or long term consequences. If appropriate reasons are given, research is justifiable despite these problems. Thus, the principle of double effect opens a way of dealing with negative and unwanted side effects in a responsible way. Research does not justify everything. But complicity is reduced to cases of voluntary and deliberate cooperation in the actions of others, which one claims to evaluate as morally wrong, (1) when there is formal inner consent, even an implicit one, which is inconsistent, (2) when the cooperation is so near and direct, that an inner rejection is not credible any more, or (3) when the damage and harm caused by the wrong action is not balanced by a proportionate high benefit.

Devolder's fifth solution shows the necessary precondition for this discussion about complicity of hiPSC research, the determination of the destruction of human embryos for research purposes as morally wrong. This judgement mostly corresponds to a personalistic position regarding the moral status of human embryos. Non-personalistic and gradualistic positions don't determine destruction of embryos as morally wrong generally or under specific conditions. Of course they don't have a problem with the discussed type of complicity. As indicated in section 2 of this chapter, the ways of justifying the destruction of human embryos haven't been able to obtain an agreement until now: Denying or weakening of the moral status and dignity of early human embryos, of research embryos or at least of surplus IVF-embryos, always contains the risk of weakening this basic ethical argument of equal human dignity in general and causing bad effects for humans in other stages of life. The second way, a justification of their destruction, as a legitimate way of killing without denying dignity of human embryos, is not convincing and may cause similar side-effects.

5. Conclusion

A consensus conferring the moral status of human embryos and the ethical evaluation of creating and destructing human embryos hasn't been achieved in the past and doesn't seem probable in the near future. Attempts to justify the destruction of human embryos for research have not succeeded in answering the ethical objections in a sufficient and convincing way. Since fundamental moral attitudes and convictions are concerned, it is adequate to impose the burden of proof on those, who advocate these ways of research. Liberty of research finds its limits where the basic moral convictions of a society are violated.

In areas of close scientific cooperation the search for agreement in fundamental ethical questions remains an urgent challenge. In a pluralistic society, despite all efforts for an ethical basic consensus, it is possible that over a longer period of time, a consensus on a certain moral question cannot be found. In such cases, the principle of tolerance is applicable only if both positions, at least, share a common basis that allows to include the contradicting positions as rational and consistent lines of reasoning. The problem is that the positions regarding the moral status of human embryos don't seem to be reconcilable within a shared basic consensus.

In this situation, the only rational way seems to be the renunciation of any further destruction of human embryos, a concentration on research with adult stem cells, iPSCs, and, where necessary, with existing hESC-lines. According to the newest developments in stem cell research, this position doesn't retard research for therapeutic objectives. It has a chance to serve as a minimal consensus and, in the long run, possibly will prove to be the better way, scientifically, ethically, in relation to social acceptability and maybe even economically.

The concern for common and strong ethical standards is part of the external responsibility of science. Science itself is dependent on social agreement and legal certainty and would suffer from a distrust and hostility towards science. In the end, there should be no difference between ethical requirements and a science that is striving for an improvement of human living conditions in a sustainable and comprehensive way: "An ethics turned towards the future and a politics of comprehensive ecological, social and humane sustainability are guided by the insight, that there cannot be a double truth. Both, ethics and politics, should be guided by the conviction that in a humane society the moral right in the long run will also be the really beneficial for humans. Though one must realistically anticipate that single groups and perhaps even societies will try to provide themselves with short-term advantages by overriding ethical boundaries, this won't be to the advantage of most people and the world of future generations" [82].

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