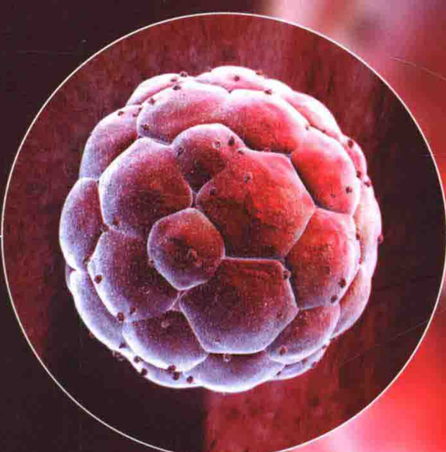
the ethics of embryonic stem cell research

Katrien Devolder



OXFORD

issues in biomedical ethics

The Ethics of Embryonic Stem Cell Research

Katrien Devolder

OXFORD
UNIVERSITY PRESS

OXFORD
UNIVERSITY PRESS

Great Clarendon Street, Oxford, OX2 6DP,
United Kingdom

Oxford University Press is a department of the University of Oxford.
It furthers the University's objective of excellence in research, scholarship, and education by publishing worldwide. Oxford is a registered trade mark of Oxford University Press in the UK and in certain other countries

First Edition published in 2015

Impression: 1

Published in the United States of America by Oxford University Press
198 Madison Avenue, New York, NY 10016, United States of America

British Library Cataloguing in Publication Data
Data available

Library of Congress Control Number: 2014942175

ISBN 978-0-19-954799-9

Printed and bound by
CPI Group (UK) Ltd, Croydon, CR0 4YY

The Ethics of Embryonic Stem Cell Research

ISSUES IN BIOMEDICAL ETHICS

General Editors

John Harris and Søren Holm

Consulting Editors

Raanan Gillon and Bonnie Steinbock

The late twentieth century witnessed dramatic technological developments in biomedical science and in the delivery of healthcare, and these developments have brought with them important social changes. All too often ethical analysis has lagged behind these changes. The purpose of this series is to provide lively, up-to-date, and authoritative studies for the increasingly large and diverse readership concerned with issues in biomedical ethics—not just healthcare trainees and professionals, but also philosophers, social scientists, lawyers, social workers, and legislators. The series will feature both single-author and multi-author books, short and accessible enough to be widely read, each of them focused on an issue of outstanding current importance and interest. Philosophers, doctors, and lawyers from a number of countries feature among the authors lined up for the series.

Acknowledgements

Writing a book is a demanding undertaking, and I could not have brought this project to a good end without the support of a number of people.

I am very grateful for the opportunities John Harris has given me throughout the years, including the opportunity to contribute to this book series. I thank him for his confidence in me, as well as for his patience, as it took somewhat longer than I expected to finish this book.

I would also like to thank those who read drafts of this work: Tom Douglas gave me several rounds of helpful comments on drafts of the whole manuscript, and these have greatly improved this book; Sam Kerstein, Jeff McMahan, Chris Megone, Freddy Mortier, Russell Powell, and Jonny Pugh offered very valuable comments on precursors to Chapter 2; Tim Davies read parts of the manuscript to check the accuracy of the scientific claims I make. (If any mistakes in the science remain they are, of course, of my own doing.) I would also like to thank Willy Lensch whose explanations of various aspects of stem cell science have been of great benefit to me. The anonymous reviewers of this book gave me much constructive feedback that helped me improve the manuscript, for which I am grateful. Parts of the book have been presented as papers at conferences and seminars, and I have profited a great deal from the comments and questions received from the audience.

The research required to write this book was generously funded by Ghent University and the Research Foundation Flanders (FWO). The Brocher Foundation in Switzerland also supported this project by awarding me a 'residency' scholarship. I have very fond memories of my stay there and would like to thank the staff for providing such a wonderful environment for academics who wish to immerse themselves in a particular project. I am also greatly indebted to Julian Savulescu and Dan Brock, who gave me the opportunity to spend time at, respectively, the Oxford Uehiro Centre for Practical Ethics and the Harvard University Program in Ethics & Health. Working in such stimulating and challenging intellectual environments contributed substantially to the quality of this work. I also wish to thank Antoine and Sylvie Winckler for their generosity. I would write another book simply to be able to work in such a wonderful setting again!

I drew on a number of published papers in writing this book, although in most cases the material was substantially reworked. These papers are: 'Killing Discarded Embryos and the Nothing-is-Lost Principle', *Journal of Applied Philosophy*, 30/4 (2013); 'Embryo Deaths in Reproduction and Embryo Research: A Reply to Murphy's Double Effect Argument', *Journal of Medical Ethics*, 39/8 (2013); 'Against the Discarded-Created Distinction in Embryonic Stem Cell Research', in M. Quigley, S. Chan, and J. Harris (eds), *Stem Cells: New Frontiers in Science and Ethics* (World Scientific Publishing, 2012); 'Complicity in Stem Cell Research: The Case of Induced Pluripotent Stem Cells', *Human Reproduction*, 25/9 (2010); 'To Be or Not to Be? Are Induced Pluripotent Stem Cells Potential Babies, and does it Matter?', *EMBO Reports*, 10/12 (2009); 'Rescuing Human Embryonic Stem Cell Research: The Possibility of Embryo Reconstitution', *Metaphilosophy*, 28/2–3 (2007); 'What's in a Name? Embryos, Entities and ANTities in the Stem Cell Debate', *Journal of Medical Ethics* 2006, 32/1 (2006); and 'Creating and Sacrificing Embryos for Stem Cells', *Journal of Medical Ethics*, 31/6 (2005).

Writing a book requires hard work and I could never have finished it without many fun moments in between. Many thanks to all my friends, and especially to Lot, Ellen, Liza, and Zus for all the good laughs. Thanks so much to my parents, who are my biggest supporters and are always there to help me in any way they can. And finally, thanks to Tom who has not only diverted me in stressful moments, but has also always strongly supported and encouraged me throughout the whole writing process. His confidence in me gave me the courage to complete this book.

Katrien Devolder

Ghent
18 February 2014

Contents

1

Introduction

The Ethics of Embryonic Stem Cell Research

1.1. The Problem

The main controversy surrounding stem cell research is not about *whether* we should use stem cells for research and therapeutic purposes—virtually everyone agrees we should—but about *what source* of stem cells we should use, and how we should obtain them. It is only the isolation and use of stem cells from early human embryos that has set off a storm of controversy and has resulted in one of the most contentious debates in bioethics: the human embryonic stem cell debate.

Most of the ethical debate about human embryonic stem cell research turns on a fundamental disagreement about how we should treat early human embryos. As it is currently done, the isolation of human embryonic stem cells involves a process in which an early embryo is destroyed. Many people accord a significant moral status to the human embryo and think that it may never simply be used in whatever way suits our research interests. Some think that human embryos (henceforth just 'embryos'—I will indicate when I refer to non-human embryos) should never be harmed or destroyed in scientific research that is not to their own benefit. At the same time there is wide agreement that embryonic stem cell research holds unique promise for developing therapies for currently incurable diseases and conditions, and for important biomedical research. It is believed that embryonic stem cell research could prevent a great amount of suffering and could improve and prolong many people's lives. This has resulted in what I will, throughout the book, refer to as

The Problem. Either one supports embryonic stem cell research and accepts resulting embryo destruction, or one opposes embryonic stem cell research and accepts that the potential benefits of this research will be foregone.

The Problem consists of a choice between two options, where, whatever option one takes, and however clear it is that one should take that particular option, one's choice will involve a significant cost as the conflicting but important value is left unsatisfied.

Of course, not everyone is confronted with the Problem. For those who believe an early embryo is merely a collection of cells, the fact that embryonic stem cell research involves destroying embryos provides no moral reason to abstain from such research. However, for those who believe the embryo has a significant moral status the Problem is very real.[1]

In this book I do not offer an exhaustive overview of all the ethical issues raised by embryonic stem cell research. I focus squarely on the Problem as it has been at the centre of the embryonic stem cell debate. Responses to the Problem have greatly influenced the regulation of stem cell research, and thus, the course this research has taken. There have been two major types of response. The first type of response has been to adopt a middle-ground position—a position between the dominant opposing views on the permissibility of embryonic stem cell research. The two dominant opposing views hold respectively that all embryonic stem cell research is morally unacceptable and that embryonic stem cell research is no more problematic than other kinds of research in cell biology. By contrast, middle-ground positions—positions between these two views—distinguish between different types or aspects of embryonic stem cell research, accepting some but not others. The second type of response to the Problem has been the development of technical solutions. Several techniques have been proposed to enable researchers to obtain embryonic stem cells, or their functional equivalents, without harming or destroying embryos.

Before I proceed with further introducing these two types of response, I should first explain the Problem in more detail. Two questions arise: (1) what moral reasons, if any, are there to support embryonic stem cell research?, and (2) what moral reasons, if any, are there to oppose it?

[1] Those who think we have moral reason to defend an ethical position that incorporates others' reasonable views may also be faced with the Problem. I will come back to this issue in Chapter 5.

1.2. Reasons for Supporting Embryonic Stem Cell Research

Beneficence

Support for embryonic stem cell research has sometimes been grounded in considerations of freedom of research[2] and scientific progress.[3] However, the main reason for supporting embryonic stem cell research is that it is expected to help us prevent and treat devastating diseases and disability. Failing to pursue embryonic stem cell research can be expected to result in much avoidable suffering and many premature deaths. It is widely accepted that we have significant moral reasons to benefit people if we can and to prevent avoidable suffering and premature death. These are reasons of beneficence.[4] The view that there are such reasons of beneficence does not rely on controversial theoretical assumptions. Indeed, it could be accepted by the proponents of all of the leading ethical theories. Plausibly, then, there are significant moral reasons for pursuing embryonic stem cell research. However, to substantiate the claim that there are such reasons, more needs to be said about what stem cells are and why they are believed to be so important.

Stem cells

Stem cells are undifferentiated cells, which means that they have not yet been committed to become 'specialized cells', that is, cells with a specific function, such as heart cells, liver cells or skin cells. The combination of two properties make stem cells different from any other type of cell in our body: (1) the capacity for continued replication while maintaining their undifferentiated state (this sort of replication is called 'proliferation' or 'self-renewal') and (2) the capacity to differentiate into various cell

[2] See e.g. ESHRE Taskforce on Ethics and Law, 'Stem Cells', *Human Reproduction*, 17 (2002), 1409–10. Thomas Heinemann and Ludger Honnefelder, 'Principles of Ethical Decision Making Regarding Embryonic Stem Cell Research in Germany', *Bioethics*, 16 (2002), 530–43. Davor Solter et al., *Embryo Research in Pluralistic Europe* (Berlin and Heidelberg: Springer-Verlag, 2003), 142.

[3] See e.g. Deutsche Forschungsgemeinschaft (German Research Foundation), 'New DFG Recommendations Concerning Research with Human Stem Cells', press release 16 (3 May 2001).

[4] Tom L. Beauchamp and James F. Childress, *Principles of Biomedical Ethics* (New York: Oxford University Press, 2001).

types of the body. One mechanism by which stem cells can replicate is asymmetric cell division, whereby a stem cell divides, producing one daughter cell like itself—a stem cell—and another more specialized daughter cell, ready for further specialization. But stem cells can also divide symmetrically. Both daughter cells will then acquire the same cell fate, and will be either stem cells or differentiated—that is, somewhat specialized—cells.

The importance of stem cells cannot be underestimated. All our body cells stem from stem cells (hence the name). In fact, each of us was once a stem cell (at least, if it is true that each of us was once a zygote[5]). A zygote is a stem cell par excellence. It is totipotent, which means that it can give rise to all the cells of the developing organism, including the placenta and other supporting tissues. After a few cycles of cell division, some cells are committed to forming the 'embryo proper', as opposed to the supporting tissues. These cells are thus somewhat more specialized than the zygote and the cells of the very early embryo. Because they can give rise to any of our body cells (and thus to all our fluids, tissues, and organs), but not the placenta and other supporting tissues, they are referred to as pluripotent stem cells. As the embryo develops further these cells will become increasingly specialized and will thus lose their pluripotency. They will become multipotent and will only be able to give rise to some types of body cell (for example, only to all types of blood cell).

Stem cells play a crucial role in our earliest development, but they are also essential later in life. Some of our organs and tissues still contain stem cells. They regularly divide and differentiate to replenish dying cells in tissues that must perpetually renew, such as the blood or the gut, and to regenerate tissues and organs that are damaged. Stem cells provide a constant supply of replacement cells, thereby serving as a repair system for the body. However, not all tissues and organs contain stem cells and not all stem cells present in the body start dividing and differentiating when an organ or tissue are damaged. The liver, for

[5] A zygote is the cell formed when a sperm fertilizes an egg. Each of us developed from a zygote, but some deny that we ever *were* zygotes (just like we were never oocytes), holding that we did not come to exist until some later point in embryonic development. See e.g. Jeff McMahan, *The Ethics of Killing: Problems at the Margins of Life* (New York: Oxford University Press, 2002).

example, regenerates quite well in response to damage, but the heart does not. This is unfortunate. If all our organs and tissues could regenerate, we could continuously repair our body and live much longer and healthier lives. This is where stem cell research comes into play: it may help us achieve this goal.

Stem cell-based therapies

One major goal of stem cell research is the development of stem cell-based therapies. The capacity of stem cells to proliferate and differentiate into various cell types of the body makes them extremely useful tools for therapy.

One stem cell-based therapy that has been routine for decades is bone marrow transplantation for the treatment of leukaemia and other blood disorders. In the 1950s, scientists discovered that bone marrow contains haematopoietic stem cells, which can give rise to all types of blood cell. Bone marrow transplantation involves the intravenous injection of these haematopoietic stem cells into a patient whose blood cells are severely reduced, or have been destroyed by high doses of chemotherapy or irradiation. The transplanted stem cells 'home' into the patient's bone marrow where they start to generate blood cells, thus replenishing the patient's blood and immune system.

Scientists interested in the therapeutic benefits of stem cells focus on two main approaches. An initial approach is to produce stem cell-derived replacement cells in the laboratory. The idea is that if a damaged tissue or organ cannot repair itself, stem cells could be obtained elsewhere. There are different sources of stem cells. Since the discovery and isolation of haematopoietic stem cells from the bone marrow, stem cells have been derived from many other organs and tissues, including peripheral blood and umbilical cord blood, placental tissues, the brain, gum tissue, the epithelia (outer layers) of the skin and digestive system, the cornea, retina, liver, teeth, and testes. Stem cells from organs and tissues from individuals after birth are *adult* stem cells, sometimes also referred to as somatic stem cells. Stem cells have also been isolated from the gametes (egg or sperm cells), tissues, and organs from aborted foetuses. These are usually referred to as *foetal* stem cells. (Note that foetal stem cells are sometimes categorized as adult stem cells, since they share many of the same features.) Finally, stem cells have been isolated from the inner cell mass of early embryos. In 1998, James Thomson's research group at the University of Wisconsin was the first to isolate and culture such *embryonic* stem cells.[6]

If a damaged tissue or organ cannot repair itself, stem cells could be obtained from these different stem cell sources. Scientists could then culture these stem cells by creating conditions that enable them to replicate many times in a petri dish without differentiating. Such a population of proliferating stem cells originating from a single parent group of stem cells is a stem cell line. Stem cells from this stem cell line could then be coaxed to differentiate into the desired cell type, and be transferred into the patient so that they can repair the damaged tissue or organ. For example, stem cells obtained from early embryos could be induced to differentiate into cardiomyocytes (heart muscle cells) to repair or replace damaged heart tissue, into insulin-producing cells to treat diabetes, or into neurons and their supporting tissues to repair spinal cord injuries. In 2010, Geron (a California based biotechnology company) conducted the first phase-I clinical trial with embryonic stem cells. Embryonic stem cell-derived oligodendrocyte progenitor cells were injected directly into the lesion site of patients with acute spinal cord injury. Oligodendrocytes are cells which support nerve cells. They can be lost in spinal cord injury, resulting in loss of myelin and neuronal function, which causes paralysis. Other clinical trials with embryonic stem cells are aimed at the development of an embryonic stem cell therapy for a rare form of juvenile blindness. The aim is to provide the patient with retinal pigment epithelium cells derived from embryonic stem cells to restore their vision.[7]

If scientists fully understood, and were able to replicate, the body's mechanisms for inducing cell differentiation, they could create whole tissues or even organs in the laboratory. There have already been reports of successful transplantation of skin, bladders, and sections of windpipes generated partly by stem cell-derived replacement cells. For example, in 2008, a woman received a new bronchus (a section of the respiratory

[6] James A. Thomson et al., 'Embryonic Stem Cell Lines Derived from Human Blastocysts', *Science*, 282 (1998), 1145–7.

[7] Raymond D. Lund, et al., 'Human Embryonic Stem Cell-Derived Cells Rescue Visual Function in Dystrophic RCS Rats', *Cloning and Stem Cells*, 8 (2006), 189–99. Bin Lu et al., 'Long-Term Safety and Function of RPE from Human Embryonic Stem Cells in Preclinical Models of Macular Degeneration', *Stem Cells*, 27 (2009), 2126–35.

tract) generated in part from her own stem cells.[8] A bronchus from a deceased donor was first stripped of cells that could cause immune reaction in the recipient and was subsequently populated with cartilage and epithelial cells produced in the laboratory from the woman's own haematopoietic stem cells. The bronchus was then successfully transplanted into the woman. Research is also being conducted into combining this sort of stem cell-based therapy with gene therapy. For example, scientists hope to treat cystic fibrosis by first inducing the patient's haematopoietic stem cells (cells that normally produce blood cells) to differentiate into airway-lining epithelial cells and then to correct, in these cells, the genetic defect that causes airway blockage in patients with cystic fibrosis. These genetically modified cells could then restore a cellular function essential to keeping the airways clear of mucus and airborne irritants.[9]

The second approach to developing stem cell-based treatments involves triggering stem cells already present in the body to migrate to and repair damaged tissues and organs.[10] Transplanted stem cells or artificial scaffolds that release biochemical factors could spur stem cells already present in the body into action. These techniques have been used in clinical trials to stimulate bone growth, cartilage, growth and heart repair. For example, a research team from Northwestern University in Chicago designed a biological material that activates bone marrow stem cells in the body to produce natural cartilage that can repair joints.[11]

Stem cell research may open up radically new ways of treating currently untreatable diseases, disorders, and injuries. Unlike currently available drugs, which mainly treat or delay symptoms, stem cells could enable us to repair or even replace damaged tissues or organs. Thus, stem cells are an extremely promising tool for regenerative medicine. However, at the time of writing, most stem cell-based therapies are

[8] Paolo Macchiarini et al., 'Clinical Transplantation of a Tissue-Engineered Airway', *The Lancet*, 372 (2008), 2023–30.

[9] Maurilio Sampaolesi et al., 'Mesoangioblast Stem Cells Ameliorate Muscle Function in Dystrophic Dogs', *Nature*, 444 (2006), 574–9.

[10] Gitte S. Jensen and Christian Drapeau, 'The Use of in situ Bone Marrow Stem Cells for the Treatment of Various Degenerative Diseases', *Medical Hypotheses*, 59 (2002), 422–8.

[11] Ramille N. Shah et al., 'Supramolecular Design of Self-Assembling Nanofibers for Cartilage Regeneration', *Proceedings of the National Academy of Sciences*, 107 (2010), 3293–8.

still in the experimental stage. Before therapeutic applications can be realized, many technical hurdles need to be overcome and many questions need to be answered, including basic questions about the mechanisms of proliferation, cell migration, and differentiation.

Biomedical research

In addition to their therapeutic promise, stem cells are potentially powerful tools for biomedical research. Scientists may be able to learn about mechanisms regulating cell growth, migration, and differentiation by observing stem cells that have been induced to differentiate into different types of body cell. A better understanding of these mechanisms could provide insight into early human development and into how tissues are maintained throughout life. It could also help us to explain how and why things sometimes go wrong in the development process, for example, in birth defects. Other major uses of stem cells in biomedical research include the creation of *in vitro* models for the study of diseases and for drug discovery and toxicity testing. Diseases could be studied or drugs could be tested on stem cells and their derivatives in a petri dish, rather than in live persons or animals. This could considerably increase the efficiency of these studies and tests, and make them safer. For example, testing the toxicity of candidate drug therapies on stem cells and their derivatives in a petri dish would avoid dangerous exposure of patients to sometimes highly experimental drugs (see section 2.1).

There is wide agreement in the scientific community that stem cell research holds the potential to significantly benefit a large number of people. It could not only prolong people's lives, but also considerably reduce morbidity. Failing to pursue this research is expected to result in many premature deaths and much avoidable suffering. As mentioned earlier, it is widely accepted that we have significant moral reason to benefit people if we can and to prevent avoidable suffering and premature death. There are thus significant reasons of beneficence for pursuing stem cell research.

However, embryonic stem cell research is but one strand of stem cell research. Are there also moral reasons for pursuing this controversial type of stem cell research in particular?

Why embryonic stem cells?

Not all types of stem cells are the same, and the differences between embryonic, foetal, and adult stem cells confer advantages and disadvantages for different uses. There is as yet no consensus on the exact characteristics and the potential of the different types of stem cell, but there is wide agreement on the following.

First, in a technical sense, embryonic stem cells are typically easier to obtain than foetal and adult stem cells. (Since foetal stem cells share many properties with adult stem cells, I will no longer mention them separately.) Embryonic stem cells are derived from embryos at the blastocyst stage. At that stage the embryo is mainly a hollow ball the size of a pinhead, with a small inner cell mass (there are no organs or blood yet—only a cluster of inner cell mass cells). A blastocyst consists of 125–250 cells, of which the inner cell mass comprises between 27 and 45 cells. Using microsurgery, researchers first remove the embryo's inner cell mass cells and then culture these cells in the laboratory to form an embryonic stem cell line. The microsurgical procedure is so invasive that it destroys the embryo's structure, thereby impeding the embryo's further development. What remains of the embryo is discarded. The procedure for deriving embryonic stem cells is relatively efficient, though derivation efficiency varies between different laboratories. Adult stem cells are generally more difficult to isolate because they are only present in small numbers. In mouse bone marrow, for example, one in 10,000 cells is a stem cell, and in humans the ratio may be even lower. Adult stem cells are also often hard, if not impossible, to harvest from the patient's organs and tissues, for example, from difficult to access organs like the heart or the brain. In most tissues there is no particular location in which stem cells can reliably be found and techniques to identify them are not efficient. Moreover, many tissues may not contain stem cells at all.

A second significant advantage of embryonic over adult stem cells is that they have a much greater proliferation capacity. Embryonic stem cells multiply readily. Under the right culture conditions they can proliferate indefinitely. With most adult stem cells, on the other hand, proliferation is slow and difficult to induce. A restricted proliferation capacity typically has negative implications for research and therapeutic applications as both require sufficient numbers of stem cells.