Stem Cell Biology and Regenerative Medicine

Kristina Hug
Göran Hermerén
Editors

Translational Stem Cell Research

Issues Beyond the Debate on the Moral Status of the Human Embryo

Humana Press

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Series Editor
Kursad Turksen, Ph.D.
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Editors
Kristina Hug
University of Lund
Department of Medical Ethics
221 84 Lund
Sweden
Kristina.Hug@med.lu.se

Göran Hermerén
University of Lund
Department of Medical Ethics
221 84 Lund
Sweden
Goran.Hermeren@med.lu.se

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Preface

For many years, the discussion of the ethical aspects of human embryonic stem cell research focused on only one question: the moral status of the embryo. It soon became clear that there were three or four different basic positions, the arguments became well-known and were discussed over and over again, and the likelihood that any interesting new arguments would appear decreased over time.

In this book, we want to show that research on human embryonic stem cells, as well as research on stem cells of other kinds, also raise other issues that deserve to be discussed, over and above the issue on the moral status of the embryo, where little progress has been made during the last decade. The various parts of this book identify such issues and discuss ways of dealing with them.

The focus of this book, as indicated by its title, is on translational stem cell research, that is, not in the first place on stem cell research aiming at new, basic knowledge of stem cell biology. Instead, the focus is on ethical, legal, and social aspects of research, which aims at paving the way for clinical applications and translating the results of stem cell research into diagnostic and therapeutic applications.

It has become increasingly clear that different diseases raise different problems and offer challenges which are not identical. The book therefore opens with a part describing the state of the art in stem cell research focusing on a number of specific diseases such as diabetes; neurodegenerative, cardiovascular, and muscular disorders; oncologic and genetic diseases; as well as treating burn victims. How far have we arrived today, and what remains still to be achieved? Important aspects include the severity of the disease, whether alternative treatments exist, and how common the disease is.

The traditional way from bench to bedside involves a number of steps: first research in vitro, then research on small animals, then on large animals, then trials of unproved treatments in emergency situations, and finally small-scale trials – and later (we are not there yet) randomized clinical trials. What do we have to have demonstrated on each of these steps in order to proceed to the next one? Some of these steps raise ethical issues that are discussed in the latter half of the first part of this book. Children, of course, raise special problems since their capacity of giving a free and informed consent is limited. These issues are discussed in Part II of this book.

In the next part, some scientific, regulatory, and ethical challenges to basic research are discussed. Human eggs are required to produce human embryonic stem cell lines, and women can be exploited or put under pressure to deliver eggs. If eggs are collected in the course of IVF treatments, problems of gratitude and psychological pressure cannot be dismissed; so the forms of obtaining informed consent become an important ethical issue. To avoid some of these problems, and diminish the demand for human ova, some scientists have made experiments by using ova from cows or rabbits to create human–animal entities for translational research. This research raises other issues that are discussed in Part III.

Stem cell banks are becoming an increasingly important resource for research. Therapeutic cloning is emerging as a costly and unlikely way to achieve clinical progress on a large scale. Against that background, stem cell banks, repositories of stem cell lines, and registries are likely to become important in the future if and when stem-cell-based therapies exist. These banks raise issues about the procurement of the tissues (information, consent, etc.); about the processing and testing necessary for safety, as well as standardization; and finally about access: who is going to have access to the samples and the information collected, on what conditions, and who is going to decide about this? Such issues are discussed in Part IV of this book.

The long and winding road from bench to bedside, via the first idea, the first experiments, via proof of concept, and proof of principle, contains many steps, requires considerable economic resources, and many things can go wrong. No university institution by itself has the resources required to develop research results into commercially viable products. Collaboration with industry is necessary. Such collaboration is not always unproblematic, as a number of disputes between scientists and industrial sponsors have indicated, and it raises also ethical and strategic issues, which are discussed in Part V of this book.

To scale up and succeed on a competitive market, first rate science and economic resources are required. But in addition to that, also intellectual property rights. Industry is not likely to be interested in investing large amounts of money in a project if there is no protection of intellectual property, and their competitors can use the results of their investments for free. The possibility to patent methods and products based on stem cell research then becomes an important issue. Controversies have surrounded a number of patent applications, particularly involving human embryonic stem cells. Praxis in different parts of the world is not the same, the US Patent and Trademark Office being more liberal than its European counterpart, the European Patent Office.

In Part VI, the legal problems raised by patents on human stem-cell-based inventions are discussed, followed by a discussion of the extent to which there can be technological solutions to a moral dilemma. Finally, in this part, ethical issues raised by stem cell patent applications including and beyond the so-called morality clause in the European Patent Convention are discussed.

Many stakeholders are involved in the future of stem cell research, not just politicians and regulators, doctors, researchers, present and future patients, and their organizations. The stakeholders also include health-care providers, research-funding

organizations, pharmaceutical industry, and taxpayers. A broad and constructive debate on the development of this rapidly developing research area is essential, particularly since recent research results (*Cell Stem Cell*, May 2010) have indicated important differences between human embryonic stem cells and induced pluripotent stem cells, suggesting that one type of cell may not in all contexts be able to replace the other.

Accordingly, communicating results and concerns has become a crucial issue, especially in research involving human embryonic stem cells. Transparency and openness have proved to be successful, and "hype" creates problems. Imaginative ways of communicating research to the general public and creating conditions for a constructive dialogue have been tried successfully and are described in Part VII.

There are a number of psychosocial and cultural factors affecting judgment and decisions about translational stem cell research. Age, gender, and culture are such factors, and it has become increasingly clear that they play a role in decision making. To neglect them would be to give a distorted picture of the complex background and would make it difficult to understand why people's views can differ so sharply. This is discussed in Part VIII of this book.

One stumbling block on the road from bench to bedside can be the evaluation of stem cell research projects in research ethics committees. Since this research is rather new and rapidly developing, it also presents challenges to the members of the research ethics committees. The systems of research ethics committee examination is not exactly the same, but international guidelines are used as a basis, like the Declaration of Helsinki and the Oviedo Convention and its protocols. The problems and procedures raised by this examination are discussed in Part IX.

In the final part, we take a look at the future of the translational stem cell research and stem-cell-based therapeutic applications. Which ethical issues are then likely to emerge? Risks, long-term effects, priority setting and social justice are such issues discussed in this concluding part.

During many years, both editors were involved in several EU-funded research projects: EuroStemCell, ESTOOLS, NeuroStemCell, Eurostemcell CA, and others. Over the years, we also learned something about the scientific aspects of the stem cell research, and we got to know many of the leading experts in the field. Finally, it is a pleasure to express our thanks to them and to all others who have contributed to this book. We also want to thank the editors at Springer for excellent collaboration in this project.

Lund, 15 May 2010

Kristina Hug
Göran Hermerén

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Editors

Göran Hermerén, Ph.D., is professor emeritus of medical ethics at the faculty of medicine, Lund University, Sweden. His current research interests and publications include priorities and allocation of resources in health care, as well as ethical aspects of genetic testing, care at the end of life, nanotechnologies, and stem cell research. Prof. Hermerén is President of the European Group on Ethics in Science and New Technologies since 2002 and the chair of the advisory board of the German Reference Center for Ethics in the Life Sciences. He is a member of the Swedish National Council on Medical Ethics and has served on many governmental and parliamentary commissions, as well as a referee for international journals. In addition, he has served as external examiner in bioethics at University College, Dublin, as a coordinator of the EU-funded research project "Euro-priorities," and is a partner in several ongoing EU-funded research projects. From 2011 she will be an external ethics advisor for the European Network "ScreenTox" (Stem Cells for Reliable, Efficient, Extended and Normalized Toxicology).

Kristina Hug, M.A., is a Ph.D. student in the Department of Medical Ethics at Lund University, Sweden. She has studied Human Rights at the Central European University in Budapest and Medical Law at the University of Essex, UK. Her current research interests include biomedical research ethics in general and, more specifically, ethical and legal aspects of stem cell research, research on vulnerable groups, as well as models and functioning of Research Ethics Committees. Kristina teaches courses in Biomedical Research Ethics at Lund University and is a faculty member in Research Ethics Advanced Certificate Program (net-based course coordinated by Vilnius University, Lithuania, Albany Medical College, and the Graduate College of Union University, USA). Kristina's working experience also includes teaching Health Law at Kaunas Medical University, Lithuania, as well as a position of a specialist in the Lithuanian Bioethics Committee. Since 2004, she has been a partner in several recent and ongoing EU-funded research projects, such as EuroStemCell, ESTOOLS and NeuroStemCell. Since May 2009, she is a member of the Editorial board of the journal "Stem Cell Reviews and Reports". From 2011 she will be an external ethics advisor for the European Network "ScreenTox" (Stem Cells for Reliable, Efficient, Extended and Normalized Toxicology).

Contributors

James A. Anderson, Ph.D., is currently a postdoctoral fellow in the Biomedical Ethics Unit at McGill University. He received his Ph.D. in Philosophy in 2007, a MA in Philosophy in 2003, and a Masters in Health Services Administration (MHSA) in 2002, all from Dalhousie University. He obtained his BA (Hons) in Philosophy from McGill University in 1998. His research interests include ethics, applied ethics (especially research ethics), philosophy of science (especially biology and clinical science), and epistemology. His current research focuses on the relationship between the epistemology of (clinical) science and the ethics of human subjects research. In particular, he is interested in the ethical and epistemological roles played by the principle of clinical equipoise. His articles have appeared in some of the leading journals in the field, including the *Journal of Medicine and Philosophy*, *Theoretical Medicine and Bioethics,* and the *Kennedy Institute for Ethics Journal.*

Peter W. Andrews, D.Phil., is the Arthur Jackson Professor of Biomedical Science and co-director of the Centre for Stem Cell Biology in the University of Sheffield. Previously, he was at the Wistar Institute of Anatomy in Philadelphia where his research focused upon the biology of human embryonal carcinoma (EC) cells, the malignant counterpart of human embryonic stem (ES) cells. His current work concerns the mechanisms by which human ES cells choose between self renewal and differentiation, and the nature of ES cell culture adaptation by which they acquire malignant characteristics reminiscent of EC cells.

Harold Ayetey, MB, BChir (MD)., after obtaining his medical and surgical degrees from the University of Cambridge in 2004, went on to pursue postgraduate training in General Internal Medicine in Cambridge, London, and Oxford, during which he developed a subspecialty interest in cardiology and the molecular basis of congenital cardiac arrhythmias in particular. In 2008, Dr Ayetey was appointed Wellcome Trust Clinical Research Fellow at the University of Cambridge and Honorary Specialty Registrar in Cardiology at Addenbrooke's Hospital in Cambridge, giving him the opportunity to combine clinical practice with a longstanding interest in stem cell biology and the concept of pluripotency. Currently, a PhD candidate in Professor Austin Smith's group at the Wellcome Trust Centre for Stem Cell Research in Cambridge, Harold's research focuses on the derivation and use of patient-specific induced pluripotent stem (iPS) cells for the study of congenital cardiac arrhythmias.

Gisela Badura-Lotter, Ph.D., is a biologist and ethicist in the field of biomedical ethics and philosophy of science. She worked as junior scientist at the Chair of Ethics in the Biological Sciences and the International Centre for Ethics in the Sciences and Humanities, both at the University of Tübingen, Germany, where she received her PhD with a dissertation on biological, medical, and ethical aspects of embryonic stem cell research. After a postdoc period at the Faculty of Medicine, at the University of Brest (France), where she worked within the EU-project

"Chimeras and hybrids in comparative European and international research – scientific, ethical, philosophical, and legal aspects," she is now assistant professor at the Institute of the History, Philosophy and Ethics of Medicine at Ulm University, Germany. She has three beloved children.

Mary Baker, MBE, is patron and immediate past president of the European Parkinson's Disease Association (EPDA), a position she was elected to in 1992 when the EPDA was first formed. Mary retired as Chief Executive of the Parkinson's Disease Society of the United Kingdom in 2001 where she had worked for 18 years. Mary is also president of the European Federation of Neurological Associations, vice president of the European Brain Council, consultant to the World Health Organization (WHO) and chair of the Working Group on Parkinson's Disease formed by the WHO in May 1997. In 2008, the Council of Europe reappointed Mary for a second term as one of the patient representatives to serve on the Management Board of the EMA, and in the same year she was appointed to the IMI JU Scientific Committee. In 2007, Mary was appointed to the Council of the ABPI and she is also a member of the ABPI Code of Practice. Other appointments include director-at-large for the World Stroke Association, former patient editor of the BMJ (now chair of the BMJ Patient Advisory Group). In 2009, Mary received the British Neuroscience Association Award for *Outstanding Contribution to British Neuroscience and for Public Service* and in 2003, an Honorary Doctorate from the University of Surrey was conferred upon her in recognition of work within the world of Parkinson's disease.

Yann Barrandon, M.D., Ph.D., is joint professor in Stem Cell Dynamics at the Ecole Polytechnique Fédérale de Lausanne (EPFL) and Lausanne University (UNIL), and head of Experimental Surgery at the Lausanne University Hospital (CHUV). He graduated as a dermatologist in Paris and obtained his Ph.D. on the long-term cultivation of human hematopoietic stem cells. He then moved to Stanford Medical School (1982–1983) as a postdoctoral fellow and then to Harvard Medical School University where he trained with Prof. Howard Green, a pioneer in epidermal stem cell biology and cell therapy (1983–1990). During this period, Yann Barrandon participated in the world's first transplantations of epidermal stem cells on extensive third-degree wounds and contributed several seminal findings, including the demonstration of stem cells in cultures of human keratinocytes. From 1990 to 2001, he was Director of Research at the INSERM and Head of Lab at the Ecole Normale Supérieure, Paris a period during which he demonstrated the presence of multipotent clonogenic stem cells in hair follicles and successfully brought epidermal stem cells from bench to bedside. Following his move to Lausanne in 2002, Yann Barrandon has explored the potency of stem cells of stratified epithelia and showed that oligopotent stem cells are present in the mammalian cornea, challenging previous dogma. He has also contributed to the characterization of several skin diseases and towards gene therapy of dystrophic epidermolysis bullosa. Yann Barrandon's present research aims (1) at understanding stem cell fate, (2) at manipulating stem cell fate, (3) to translate cell and gene therapy from the bench to bedside. He was a PI in EuroStemCell, Therapeuskin (FP6), and is a partner in several

FP7 EC stem cell consortia (EuroSystem, Optistem, and BetacellTherapy); he was elected an EMBO member in 2009.

Linus Broström, Ph.D., is a postdoctoral research fellow at the Department of Medical Ethics, Lund University, Sweden, and at the Vårdal Institute, the Swedish Institute for Health Sciences. He received his PhD in 2007, with a thesis on substituted judgment. Since then, he has been doing research on a variety of issues in bioethics, especially the ethics of surrogate and end-of-life decision making. He is a government-appointed substitute member of the Regional Ethical Review Board in Lund, and currently his teaching at the faculty of medicine is mainly on research ethics.

Oliver Brüstle, M.D. Ph.D., is professor of Reconstructive Neurobiology at the University of Bonn. He is also co-founder and scientific director of LIFE & BRAIN GmbH, a biomedical enterprise serving as translational hub of the University of Bonn Medical Center. Trained as an M.D., he conducted research and clinical work in neuropathology and neurosurgery at the universities of Zurich and Erlangen, respectively. In 1993 he joined the laboratory of Ron McKay at the National Institutes of Neurological Disorders and Stroke in Bethesda, MD, USA to study neural stem cells. Upon his return to Germany in 1997, he started is own lab and, in 2002, became director of the newly founded Institute of Reconstructive Neurobiology. His field of interest is stem cell research, with a focus on stem-cell-based brain repair. The Brüstle lab has particular expertise in the generation of neural cells from pluripotent stem cells and their application in models of neurological disease. Having been the first researcher working on human embryonic stem cells in Germany, he was instrumental in shaping the public debate around this sensitive topic and became a fierce political advocate of stem cell research. In 2000, Oliver Brüstle received the Bennigsen-Foerder Award. Since 2002, he serves as chair of the Steering Committee and board member of the Stem Cell Network North Rhine Westphalia. He is editorial board member and referee for several scientific journals and reviewer for numerous funding agencies. Since 2008, he also serves on the boards of directors of the multinational European research consortia ESTOOLS and NEuroStemCell.

Anders Castor, M.D., Ph.D., is senior consultant in pediatric oncology at Skane university hospital. He has a Ph.D. in malignant stem cell research from Lund university. Anders has, partly due to the clinical experiences within the field of pediatric oncology, developed a strong and broad interest in medical ethics, with a focus on ethics and children. He has initiated, and is currently chairing two different ethical committees: one at the department of pediatrics at Skane university hospital, Lund, which focuses on consultative services and the other a joint Nordic committee, with clinically active pediatric oncologists and nurses from all the Nordic countries, which focuses on developing competence and guidelines in the field of pediatric oncology. He is also doing research on ethical decision-making with regard to children.

Neville Cobbe, Ph.D., is currently a research fellow at the University of Liverpool, having previously worked for several years at the University of Edinburgh. His main research interests have been the evolutionary and functional analysis of proteins that contribute to chromosome behavior, cell division, and cell migration. Aside from research publications in genetics and cell biology, Neville has been interested in various aspects of communicating science and its relevance to society, organizing exhibitions for the Edinburgh International Science Festival over successive years and participating in workshops for young people or adults on various bioethical issues (ranging from genetic testing to cloning). This has led to invitations to give public presentations on stem cell research to diverse audiences on behalf of the UK Research Councils, the Scottish Council on Human Bioethics, and the Royal Society of Edinburgh, as well as contributing oral and written evidence to the House of Commons Science and Technology Select Committee.

Giulio Cossu, M.D. Ph.D., Giulio Cossu has a long lasting interest in the field of muscle cell and developmental biology and in the cell therapy of muscular dystrophies. He received his MD degree from the University of Rome in 1997. He trained as a Fogarty postdoctoral at the Wistar Institute, University of Pennsylvania (1980–1983), and then became associate and then full professor at the Dept. of Histology and Medical Embryology of the University of Rome "La Sapienza." In 2000 he was appointed director of the "Stem Cell Research Institute" of the Hospital San Raffaele in Milan. Since 2005 he is professor of histology and embryology at the University of Milan. In 2008, he was appointed director of the newly created San Raffaele Division of Regenerative Medicine. Since 1997 Giulio Cossu is EMBO Member; he has been president of the Italian Association of Cell and Developmental Biology (1998–2001) and member of the Directory Board of the International Society for Stem Cell Research (2003–2005). Giulio Cossu is currently a member of the Directory Board of the International Society for Differentiation and senior editor of EMBO Molecular Medicine. He is currently serving as chairperson for Panel LS7 (Molecular Medicine) for the European Research Council. He is also member of the ISSCR Task force for Clinical Translation of Stem Cell Research.

Marcus Düwell, Ph.D., holds a chair for philosophical ethics at the Department for Philosophy at Utrecht University. He is research director of the Ethics Institute of Utrecht University, director of the Netherlands Research School for Practical Philosophy and director of the Leiden-Utrecht Research Institute ZENO. From 1993–2001 he was academic coordinator of the Interdepartmental Center for Ethics in the Sciences and Humanities at the University of Tübingen. His research interests include bioethics (especially ethics of genetics, environmental ethics) and basic questions of moral philosophy (foundations of individual rights, human dignity) and the relation between ethics and aesthetics. He is editor-in-chief of the book series "Ethics and Applied Philosophy" (Springer publisher).

Sebastién Duprat, M.Sc., is director of business development & partnerships, and leads the communication unit for the I-STEM institute in Evry (Paris), France. After his graduation in biology of health (University of Lille, France) he performed

fundamental research on adult neural stem cells in the Viikki Biocentre (University of Helsinki, Finland). Constantly looking for cross-disciplinary activity, he moved to the University of Sheffield, UK to be training and outreach manager of a European Commission-funded research consortium on human embryonic stem cells (ESTOOLS) spanning across ten countries of the European Research Area. He has published two books in French (philosophy and poetry) and a number of articles on a variety of topics.

Petr Dvořák, Ph.D., is professor of molecular biology and genetics at Masaryk University, Brno, Czech Republic. He is the head of Department of Biology, one of the key research departments of Faculty of Medicine where he also serves as the vice dean for research. He has been involved in the Czech dialogue on embryonic stem cell policy since 2003 when his group derived several lines of human embryonic stem cells. Petr Dvořák is interested in growth factor signaling in human embryonic cells, as well as induced pluripotent stem cells and several specific topics related to their differentiation, genomic stability, and use for drug development. He has published many research articles and reviews in the biology of embryonic stem cells and has worked on several national and international projects focused on development of tools for medical application of stem cell research and contextual regulatory issues.

Melissa L. Finucane, Ph.D., is a senior fellow at the East-West Center in Honolulu, Hawaii. Dr Finucane conducts empirical research to clarify the mechanisms underlying human judgment and decision processes and their implications for public policy making. Her work focuses on the interplay of affect and cognition and the role of sociocultural factors in judgment and decision processes under conditions of uncertainty. Dr. Finucane received the Australian Skeptics Eureka Prize for Critical Thinking in 1999 and has received funding for her research from the National Science Foundation, the National Institutes of Health, and other organizations. She has published in numerous peer-reviewed journals, including *Journal of Behavioral Decision Making, Risk Analysis,* and *Social Science and Medicine.* Dr. Finucane is a member of the Society for Judgment and Decision Making.

Michael Fuchs, Ph.D., is the general manager and a senior scientist at the Institute of Science and Ethics in Bonn (IWE). Since 1995, he teaches philosophy at the University of Bonn. He is the representative of the IWE at the Board of Directors of the European Association of Centers of Medical Ethics since 2000. He functions as partner and project leader in several European and national research projects on bioethics and research ethics. Recently he has published books and articles on enhancement technologies, national ethics councils, research ethics, gene therapy, and genetic diagnosis. His other fields of research are philosophy of nature, anthropological and ontological problems of individuation and individuality of living beings, semiotics and philosophy of language, and medieval Latin philosophy.

Nicolas Grasset, M.D., Ph.D., graduated from Lausanne Medical School in 1999 and was a surgical resident before joining the Barrandon's laboratory in 2003. He obtained his PhD in Life Sciences and Technology at the Ecole Polytechnique

Fédérale de Lausanne (EPFL) in 2008. His research, supported by the FP6 EuroStemCell consortium, consisted in validating the pig as a predictable animal model to understand the fate of autologous epidermal stem cells transplanted in extensive wounds. Besides a strong interest in ethics, Nicolas Grasset aims at bringing stem cells from bench to bedside.

Manal Hadenfeld, Ph.D., is a biologist, currently working at LIFE&BRAIN GmbH, which is a technology transfer platform for the University of Bonn in the field of Biomedicine. At LIFE&BRAIN, she is perusing different projects on industrial applications of stem cells as well as public outreach projects related to stem cell technologies. Earlier, she worked and published as a scientist in the fields of stem cell engineering and protein biochemistry at the Universities of Bonn and Cologne, Germany.

Mattias Hansson, Ph.D., is head of the department of Stem Cell Biology at the Hagedorn Research Institute, which is an integrated R&D component of the global diabetes healthcare company Novo Nordisk. His research is focused on the development of cell replacement therapy for the treatment of diabetes mellitus with particular interest in translational stem cell research. Dr. Hansson has a M.Sc. in chemical engineering from Lund University, Sweden, and a Ph.D. from the University of Copenhagen, Denmark, where he was a Marie Curie fellow.

Mette Hartlev, Ph.D., LL.D., is professor of medical law at the Faculty of law, University of Copenhagen. Her research interests focus on health law and patient's rights, including human rights and protection of vulnerable patients. Furthermore, she has done research within the field of biolaw , bioethics and law, and science and technology studies. She has published extensively on issues such as patients' rights, medical research, artificial reproduction, gene technology, biobanks, and stem cell research. Mette Hartlev has participated in several research projects funded by the EU-Commission and has been a member of the Danish Council of Ethics (2000–2005) and the Nordic Committee on Bioethics (2003–2007).

Matthew Herder, B.Sc.(hons.), LL.B., LL.M., J.S.M., is an Assistant Professor in the Department of Bioethics, Faculty of Medicine, at Dalhousie University. He holds a Master of the Science of Law degree from Stanford Law School, law degrees from Dalhousie University, and a science degree from Memorial University. Matthew's research focuses on how intellectual property rights (especially patent rights) and the emphasis placed upon commercializing early-stage, publicly funded research impacts academic scientists, science, and society.

Outi Hovatta, M.D. Ph.D., is a professor of obstetrics and gynaecology at the Karolinska Institutet, Stockholm, Sweden, since 1998. She has a long research career in infertility and assisted reproduction, first in Helsinki Finland, then during 1995–1998 in the Imperial College at Hammersmith Hospital. Genetic causes of infertility, maturation of human ovarian follicles and oocytes in vitro, and, since 2002, derivation of new human embryonic stem cells lines, improving the quality of such lines towards clinical grade have been her main research activities. She has

also established induced pluripotent cells, and improved derivation and culture conditions of pluripotent stem cells. She has published some 300 articles and book chapters from the topics. In addition, she has written a large number of articles for general public regarding these topics.

Mats Johansson, Ph.D., is associate professor at the Department of Medical Ethics, Lund University. He holds a Ph.D. in practical philosophy. His work has centered on empathy and, more recently, the ethics of surrogate decision making. Dr. Johansson is currently working as a researcher at the Vårdal Institute, The Swedish Institute for Health Sciences.

Jonathan Kimmelman, Ph.D., holds a Ph.D. in molecular biophysics and biochemistry and is assistant professor in the Social Studies of Medicine/ Biomedical Ethics Unit at McGill University. His research centers on the ethics of translational clinical research – especially involving novel medical interventions like gene transfer and cell transplantation. His book, *Gene Transfer and the Ethics of First-in-Human Research: Lost in Translation* (Cambridge University Press, 2009), is the first full-length analysis of the ethics of translational clinical research and has been described as "set[ing] a new standard for bioethical scholarship that is at once scientifically well-grounded, politically astute, philosophically original, and a pleasure to read." Kimmelman was the winner of the 2006 Maud Menten New Investigator Prize (Institute of Genetics). He chairs the ethics committee of the American Society of Gene and Cell Therapy, and serves on the CIHR Stem Cell Oversight Committee and the NHLBI Gene and Cell Therapy Data Safety Monitoring Board.

Zaal Kokaia, Ph.D., is professor of experimental medical research at the Division of Neurology, Department of Clinical Sciences, Lund University Hospital, and Coordinator of Strategic Research Area in Stem Cells and Regenerative Medicine (STEMTHERAPY). He has served as coordinator of EU-sponsored integrated project StemStroke 2006–2009. He is visiting professor at Tbilisi State University and in 2009 received Peter Sarajishvili Medal from Georgian Association of Neurologists and Neurosurgeons for his contribution in neuroeducation. He has published more than 100 scientific papers and served as reviewer for many international journals and granting agencies. Current research interests in Kokaia's laboratory are the generation and characterization of neural stem cell lines from different sources and development of stem-cell-based treatment for stroke.

Olle Lindvall, M.D., Ph.D., is professor of clinical neurology and chairman of the Division of Neurology at the University Hospital, Lund, Sweden. He has served as vice-dean of the Medical Faculty at the University of Lund 1997–1999, member of the Board of the Swedish Research Council (medical division) 2001–2006, and clinical coordinator in EU-sponsored integrated project EuroStemCell 2003–2007. He has received numerous prizes and awards. Dr. Lindvall is, since 2004, member of the Board of the International Society for Stem Cell Research (ISSCR), and since 2005 member of the Board of Reviewing Editors for SCIENCE and member of the Scientific Advisory Board of the Michael J. Fox Foundation

for Parkinson's Research. He was co-chair of the ISCCR Task Force on the Clinical Translation of Stem Cells 2007–2008. According to PubMed, Lindvall has about 300 published articles since 1972. In 2008, Lindvall was elected member of the Royal Swedish Academy of Sciences. Lindvall has headed the clinical neurotransplantation program at the University of Lund since 1983. This program has pioneered cell replacement strategies and been the first to show that transplanted neurons can survive, grow, restore transmitter release, become functionally integrated, and give rise to clinically measurable improvements in the diseased human brain. Current research interests in Lindvall's laboratory are the development of stem-cell-based treatments for Parkinson's disease and stroke, especially the regulation and therapeutic relevance of neurogenesis from the adult brain's own neural stem cells.

Ole Dragsbæk Madsen, Ph.D., is professor, vice-president and director, Beta Cell Biology at Hagedorn Research Institute (HRI), Gentofte, Denmark. HRI is fully owned by Novo Nordisk A/S, a world leader in diabetes therapy. Madsen is a member of the Novo Nordisk R&D Bioethics Board. HRI is an early applied research unit that within its mission also works to find a cure for diabetes and its complications. Madsen has trained in biological sciences at University of Århus, Denmark and University of Chicago, USA and started building a research team at HRI based on his discoveries of some of the first multipotent pancreatic endocrine cell lines, which he established during his stay at University of Chicago. The cell cultures provided the first model by which (1) insulin gene activation could be studied during beta-cell maturation, (2) both insulin and glucagon cell lineages could be derived from common progenitors, and (3) derived tumor models served as tissue for starting the building of transcription factor hierarchies in islet endocrine development. A long-term goal is to translate knowledge from developmental biology to ex vivo/in vivo formation/expansion of a functional beta-cell mass as the ultimate treatment of diabetes. Reestablishments of an adequate functional beta-cell mass to restore euglycemia is the most promising future therapy of diabetes – predicted to eliminate the risk of developing devastating late complications.

Kate M. Millar, Ph.D., is director of the Centre for Applied Bioethics, School of Biosciences and School of Veterinary Medicine and Science, University of Nottingham. She is currently vice president of the European Society for Agricultural and Food Ethics (EurSafe). Her research focuses on the ethical issues raised by the application of biological knowledge to the use of animals, agri-food production, and environmental management. She has a particular interest in biotechnology ethics, and the development and application of ethical frameworks and stakeholder participatory methods.

Christine Mummery, Ph.D., is professor of Developmental Biology at Leiden University Medical Centre where she is chair of the Department of Anatomy and Embryology. She studied physics and has a Ph.D. in biophysics from the University of London. She received a postdoctoral fellowship from the Royal Society (UK) for research at the Hubrecht Institute in the Netherlands where she was senior

group leader and professor of cardiac development. Her early research concerned TGFβ signaling in mouse development and differentiating stem cells. She started working with human embryonic stem cells in 2000 and derived the first lines in the Netherlands in 2003. After moving to Leiden in 2008, she continued research in both developmental biology of the heart and the differentiation of pluripotent human embryonic stem cells and iPS cells into the cardiac and vascular lineages. Functional characterization of the stem cell derivatives is presently the major focus of her lab, immediate interest being on the use of human pluripotent stem cells as disease models, for drug discovery and in future cardiac repair. In 2007, she spent sabbatical leave as a joint Harvard Stem Cell Institute/Radcliffe fellow. She presently serves on the Ethical Councils of the Royal Netherlands Academy of Science and the Ministry of Health, providing specialized advice on research with human embryos and embryonic stem cells. She is a member of the Scientific Advisory Boards of multiple stem cell institutes and research programmes, has written a popular book on stem cells and is editor/on the editorial board of Stem Cell Research, Cell Stem Cell, Stem Cells and Differentiation. She is president of the International Society of Differentiation and on the board of the International Society of Stem Cell Research and an elected member of the Royal Netherlands Academy of Arts and Science.

Aliki Nichogiannopoulou, Ph.D., studied biology and philosophy at the Albert-Ludwigs-University in Freiburg, Germany and did her diploma thesis in molecular immunology at the Max-Planck-Institute of Immunology in Freiburg. She did her Ph.D. thesis on adult, fetal, and embryonic stem cells in the Department of Genetics at Harvard Medical School in Boston, and did her postdoctoral research on stem cells at Harvard Medical School in Massachusetts General Hospital. She became a patent examiner at the European Patent Office in September 1998 and joined the Patent Law department in 2004. She was holding a joint appointment in the two departments until December 2009. She participated in all major stem cell cases at the European Patent Office and represented the President of the Office in front of the Office's Enlarged Board of Appeal in the Thomson case on human embryonic stem cells. She has represented the Office in patent law, scientific and ethical conferences and workshops, and has lectured on the legal and ethical aspects of stem cell patenting at several occasions. In January 2010, she was appointed director in Biotechnology at the European Patent Office.

Ubaka Ogbogu, LL.B, LL.M., is a doctoral candidate in the Faculty of Law, University of Toronto. His doctoral research is supported by prestigious fellowships from the Canadian Social Sciences and Humanities Research Council and the Lupina Foundation's Comparative Program on Health and Society. Ubaka has done significant research on the ethical, legal, and social issues associated with emerging biotechnologies, and his doctoral dissertation examines the historical role of law in the resolution of biomedical controversies with political, moral, or ethical overlays.

Johannes Persson, Ph.D., is associate professor and senior lecturer at the Department of Philosophy, Lund University. He holds a Ph.D. in Theoretical

Philosophy (Causal Facts, Stockholm: Thales, 1997), specializing in theories of causation and some central applications of causal concepts. His recent research focuses on metaphysics, philosophy of science, decision-making, and risk. He does much of his teaching on these subjects too.

Michael Roßbach, Dr. (*1978), is Assistant Professor at the National University of Singapore (NUS) and a member of the Faculty of Sciences since January 2008. In Singapore, he is a senior lecturer at the German Institute of Science and Technology, a subsidiary of the Technical University of Munich, Germany. He is a fellow of the German National Academic Foundation, the Westphal Foundation and the Dr. Meyer-Struckmann Foundation.

Michael Roßbach completed his undergraduate studies of biology and chemistry at the University of Bonn and the University of New South Wales, Sydney, Australia, and obtained his master's degree and PhD. from the Private University of Witten/Herdecke, Germany. He was a research fellow at the CBR Institute for Biomedical Research at Harvard Medical School and a post-doctoral fellow at the Genome Institute of Singapore. His scientific interests include gene regulation in stem cells with an emphasis on neuroscience, oncology and translational research. Michael Roßbach has published his work in various journals and books and was awarded the Klee Prize for his contributions to the field of medical technologies and the Raiffeisen Prize of State of Rhineland-Palatinate in Germany.

From 2009–2010, Michael Roßbach was a senior scientist at the Institute of Reconstructive Neurobiology at the University of Bonn, Germany, and the Business Development Manager of the LIFE&BRAIN GmbH in Bonn. Michael Roßbach is a board member of several Private Equity and VC-/Consulting businesses and partner in two biotech companies. From January 2011, he joins the Genome Institute of Singapore (GIS) again as the newly appointed Scientific Program Manager.

Nils-Eric Sahlin, Ph.D., is professor and chair of medical ethics, Faculty of Medicine, Lund University. He is a former professor of theoretical philosophy, Lund University and working member of The Royal Swedish Academy of Letters, History and Antiquities. Dr. Sahlin has authored and edited several books on various topics. He is in particular interested in probability theory, decision theory and philosophy of risk.

Douglas Sipp, Ph.D., after working in the software and publishing industries in Tokyo, joined the RIKEN Center for Developmental Biology in 2002 as manager of the Office for Science Communications and International Affairs. In 2009, he was appointed to head the Science Policy and Ethics Studies unit at the same institute. He additionally serves as a communications advisor at the Kyoto University Center for iPS Research and Application. He served as Chair of the International Committee of the International Society for Stem Cell Research from 2005 to 2009. He is secretary-treasurer of the Asia-Pacific Developmental Biology Network and the Asia Reproductive Biotechnology Society, as well as business manager of the International Society of Developmental Biologists and the Stem Cell Network: Asia-Pacific. He is a member of the International Stem Cell Forum

Ethics Working Party, and international coordinator for the Japanese Society of Developmental Biologists.

Glyn Stacey, Ph.D., was originally educated and trained as a microbiologist in the public health sector, moved into cancer research and then worked on the development of cell substrates for a variety of public health issues including vaccine production and testing. At his current Institute (NIBSC) he has established the Division of Cell Biology and Imaging with a portfolio of health related work on cell cultures used for manufacturing and provision of reference materials for genetic testing. More recently he has been responsible for the establishment of the UK Stem Cell Bank, a publicly funded resource, which assures the availability of ethically sourced and well-characterized human stem cell lines for international supply for research and clinical trials. He is an advisor to the WHO and a number of national regulators. Glyn leads the International Stem Cell Banking Initiative with representation from 20 countries and chairs the scientific advisory board for a Public–Private Partnership called Stem Cells for Safer Medicine.

Jeremy Sugarman, MD, MPH, MA is the Harvey M. Meyerhoff Professor of Bioethics and Medicine, professor of medicine, professor of Health Policy and Management, and deputy director for medicine of the Berman Institute of Bioethics at the Johns Hopkins University. He is an internationally recognized leader in the field of biomedical ethics with particular expertise in the application of empirical methods and evidence-based standards for the evaluation and analysis of bioethical issues. His contributions to both medical ethics and policy include his work on the ethics of informed consent, umbilical cord blood banking, stem cell research, international HIV prevention research, and research oversight. Dr. Sugarman is the author of over 200 articles, reviews and book chapters. He has also edited or co-edited four books (*Beyond Consent: Seeking Justice in Research; Ethics of Research with Human Subjects: Selected Policies and Resources; Ethics in Primary Care; and Methods in Medical Ethics*). Dr. Sugarman is an associate editor of *Clinical Trials*, a contributing editor for *IRB*, and is on the editorial boards of several academic journals. Dr. Sugarman currently serves on the Maryland Stem Cell Research Commission, the Scientific and Research Advisory Board for the Canadian Blood Service and the Ethics and Public Policy Committee of the International Society for Stem Cell Research. He is co-chair of the Johns Hopkins' Institutional Stem Cell Research Oversight Committee. In addition, he is chair of the Ethics Working Group of the HIV Prevention Trials Network and is the ethics officer for the Resuscitation Outcomes Consortium. Dr. Sugarman has been elected as a member of the American Society of Clinical Investigation and the Institute of Medicine. He is a fellow of the American Association for the Advancement of Science, the American College of Physicians and the Hastings Center.

Jochen Taupitz, Ph.D., professor, studied law in Göttingen and Freiburg from 1973–1978. He received his doctoral degree from the University of Göttingen in the year 1981, passed the higher state examination in law in 1982 and became a university lecturer in Göttingen. In 1988 he received his habilitation from the University of

Göttingen with a postdoctoral thesis on the professional codes of ethics. From 1988 to 1989, he was a university professor in Göttingen. Since 1990 he has held the position of a full professor for civil law, civil procedure law, private international law and comparative law at the University of Mannheim. From 1996 to 2002 he also performed secondary duties as a judge at the Higher District Court (Oberlandesgericht) of Karlsruhe. In addition, since October 1998, he has been the Managing Director of the Institute for German, European and International Medical Law, Public Health Law and Bioethics of the Universities of Heidelberg and Mannheim.

Among other appointments, he is a member of the German Ethics Council (and was a member of the former National Ethics Council), member of the Board of Directors of the Central Ethics Committee at the German Medical Association, member of the Ethics Committee for the Medical Faculty of Heidelberg University, member of the Board of Directors of the German Association of Medical Ethics Committees, head of the Advisory Council on Questions of Principle of the German Association of Medical Ethics Committees, vice president of the Academy for Ethics in Medicine, and member of the European Academy of Sciences and Arts. His main fields of research are medical law and public health law, combined with bioethics. He has published more than 440 books and articles.

Paul L.C. Torremans, Ph.D., professor, taught at the Universities of Leicester and Leeds, before joining the University of Nottingham in September 2002. He also served as a sub-dean for graduate studies at the Faculty of Law of the University of Leicester. His areas of expertise are Intellectual Property Law and Private International Law. In relation to the latter area, Professor Torremans was also a member of the Department of Private International Law of the Faculty of Law of the University of Ghent, Belgium until 30th September 2008. Professor Torremans is a member of the Association Littéraire et Artistique Internationale (ALAI) and chairman of its British branch BLACA. He is also a member of the Association for the Enhancement of Teaching and Research in Intellectual Property – ATRIP (the worldwide association of teachers and researchers in intellectual property). Professor Torremans has acted as an expert for the World Intellectual Property Organization, the European Commission (most recently on 21st April 2009 for the European Group on Ethics in science and new technologies in relation to synthetic biology patents), the European Patent Office and other international organizations. He is also a member of CLIP, an international group of experts developing a set of principles on the interaction between intellectual property and private international law.

Niklas Vareman, M.A., is a Ph.D. student in theoretical philosophy, Lund University. Vareman's philosophical interests lie in decision theory and theory of knowledge. His work as a PhD student is part of a risk research project funded by the Swedish Research Council.

Philip Watson, Ph.D., has 20 years of international clinical research experience within the pharmaceutical industry including companies such as Wellcome Research Laboratories, SmithKline Beecham and Roche. He now works in Safety Risk Management at Roche products Ltd., responsible for biologic therapies within

the Inflammatory therapeutic area. He has previously participated in multiple filing teams for successful regulatory applications for biologic therapies in inflammatory disease and oncology. He currently leads a group of physicians and scientists responsible for anti CD20 biologic therapies at Roche. Phil has also worked extensively within the anti-infective therapeutic area and has a longstanding interest in medical informatics having completed an MSc in this field and has gained further experience of the application of computer assisted approaches to drug disease modeling and clinical trial design. He has also undertaken extensive work as consultant in the field of healthcare and scientific consultancy, including work undertaken for the European Commission. He received his medical degrees from St. Mary's Medical School in London and was subsequently elected a collegiate member of the Royal College of Physicians, following training in and rotation through the major medical specialties. He was registrar in respiratory medicine at the Royal Brompton Hospital prior to joining the pharmaceutical industry. He then went on to complete the Diploma in Pharmaceutical Medicine, following which he was elected Member, and more latterly, Fellow of the Faculty Pharmaceutical Medicine. He has also completed a year long post graduate course in Health Economics. He participates actively in various safety related strategies within Roche and actively collaborates with academics, regulators and patient advocates in order to pursue these.

Andrew E. Williams, Ph.D., is a psychologist and an investigator at the Kaiser Permanente Center for Health Research, Hawaii. His research focus is on understanding patterns of care using electronic medical record data in order to improve point-of-care medical decision support. He holds an academic appointment at the Department of Public Health Sciences at the University of Hawaii's John A Burns School of Medicine.

Valerie Wilson, Ph.D., is a reader in developmental biology at Edinburgh University. Her area of expertise is in mammalian embryonic development; in particular, the generation of the musculoskeleton and spinal cord by a population of tissue stem cells. She has also been involved in various science communication and ethics ventures, including the short film series "Stem Cell Stories" funded by the European Consortium "Eurostemcell," the 2006 Church of Scotland report on human embryonic stem cells, and the 2007 House of Commons Science and Technology committee report on human-animal chimeric and hybrid embryos.

Amy Zarzeczny, L.L.M., is a research associate and project manager at the University of Alberta's Health Law Institute (HLI). In that capacity, Ms. Zarzeczny is involved in a number of large international, interdisciplinary and collaborative research projects. Her work is primarily focused on examining ethical, legal, social and policy implications of emerging biotechnologies including stem cell research, neuroimaging and genetics. Ms. Zarzeczny has published a number of papers on these topics. Prior to joining the HLI, Ms. Zarzeczny practiced law with Reynolds, Mirth, Richards & Farmer LLP in Edmonton, Alberta. She holds a Master of Laws from the London School of Economics and Political Science.

Part I: Translational Stem Cell Research: What is Possible Today and What Still Remains to be Achieved?

Chapter 1
Towards Clinical Application of Stem Cells in Neurodegenerative Disorders

Olle Lindvall and Zaal Kokaia

Abstract Stem cells have the capacity to generate neurons and glia cells which are lost in neurodegenerative diseases such as Parkinson's disease and stroke. The adult brain's own neural stem cells are potential novel therapeutic targets because they produce neurons and glia in response to injury and could become affected by the degenerative process. Besides cell replacement, stem cell-based approaches can also improve function by modulating inflammation, preventing neurons from dying, and increasing angiogenesis. These exciting laboratory findings should now be responsibly translated to the clinic. However, the development of stem cell-based therapies for human neurodegenerative diseases will require major research efforts so that the mechanisms regulating the proliferation, migration, differentiation, survival and function of stem cells are much better understood and can be effectively controlled. Strategies to prevent tumor formation must be developed. Finally, the functional efficacy of stem cells or their derivatives, their mechanisms of action, and absence of significant adverse effects should be demonstrated in animal models with pathology and symptomatology resembling the human disease.

Keywords Parkinson's disease • Alzheimer's disease • Stroke • Neurogenesis • Transplantation

1.1 Introduction

Neurodegenerative diseases comprise a wide range of human conditions in which neurons and glial cells in the brain and spinal cord are lost. In acute neurodegenerative diseases, different types of neurons and glial cells die within a restricted brain area

O. Lindvall (✉)
Laboratory of Neurogenesis and Cell Therapy, Wallenberg Neuroscience Center, University Hospital, SE-221 84, Lund, Sweden
and
Lund Stem Cell Center, Lund, Sweden
e-mail: Olle.Lindvall@med.lu.se

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over a short period of time, e.g., in response to ischemic stroke or spinal cord injury. In chronic neurodegenerative diseases, there is over several years either a rather selective loss of a specific cell population, such as dopamine (DA) neurons in Parkinson's disease (PD) or motor neurons in amyotrophic lateral sclerosis (ALS), or a widespread degeneration of many neuron types, such as in Alzheimer's disease (AD). Stem cells may preserve and restore function in several different ways, e.g., by releasing trophic molecules or modulating inflammation. However, the most attractive possibility would be if they could be used to replace the cells that have died. This could be achieved either by transplantation of stem cell-derived cells predifferentiated in vitro to various stages of maturation, e.g., to neuroblasts, or by stimulation of the formation of neurons and glia from the adult brain's own neural stem cells (NSCs). No stem cell-based treatment has yet been established for any neurodegenerative disorder. Despite this, "treatments" for several of these diseases are offered at "clinics" around the world, without rationale and with poor scientific and clinical basis. The vast majority of these sites over-promised the results and gravely underestimated the potential risks [1]. "Stem cell tourism" is a major problem in the field of neurodegenerative diseases that damages patients and their relatives and slows down the serious development of effective stem cell-based therapies [2]. For the responsible application of stem cell therapies in patients with neurodegenerative diseases, it is now important to define clinical road maps, i.e., the major milestones in basic and clinical research that need to be reached, and the ethical, regulatory, societal and economical issues that need to be addressed. In this chapter, we will discuss some general issues related to the clinical translation of stem cells. We will also describe the current status of stem cell-based approaches and define the critical milestones that remain to reach the clinic in three neurodegenerative disorders – PD, AD, and stroke.

1.2 Moving Stem Cells to the Clinic in Neurodegenerative Disorders: General Aspects

When considering the application of stem cells in patients with a specific neurodegenerative disorder, it must be understood what the acceptable risks are and what will be necessary for this approach to be clinically competitive. Stem cells and their derivatives represent, in most cases, entirely novel products. Proliferation and maturation of stem cells are difficult to control. Animal models may not fully predict their toxicity, occurrence of immune and other biologic responses, and risk for tumor formation after implantation in patients. It should also be underscored that the degree of disability and available therapeutic options differ widely between various neurodegenerative diseases. Patients with PD have virtually normal life expectancy, motor symptoms are effectively reversed during the first years by several drugs, and valuable improvement can be obtained in advanced stages as well. In contrast, for patients with ALS, which is a fatal disorder, there is currently no effective treatment. If efficacious therapy already exists, as in PD, the risk must be low and the stem cell-based approach must offer an advantage (e.g., better functional outcome and single procedure versus life-long drug therapy with associated side effects). If effica-