Stem Cells in Clinical Applications

Phuc Van Pham *Editor*

Stem Cell Processing

Springer

Stem Cells in Clinical Applications

Series Editor
Phuc Van Pham
Laboratory of Stem Cell Research and Application
University of Science
Vietnam National University
Ho Chi Minh City, Vietnam

More information about this series at http://www.springer.com/series/14002

Phuc Van Pham
Editor

Stem Cell Processing

Springer

Editor
Phuc Van Pham
Laboratory of Stem Cell Research and Application
University of Science
Vietnam National University
Ho Chi Minh City, Vietnam

ISSN 2365-4198 ISSN 2365-4201 (electronic)
Stem Cells in Clinical Applications
ISBN 978-3-319-40071-6 ISBN 978-3-319-40073-0 (eBook)
DOI 10.1007/978-3-319-40073-0

Library of Congress Control Number: 2016951718

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG Switzerland

Preface

The term “stem cell” appeared in the scientific literature as early as 1868 in the work of the eminent German biologist Ernst Haeckel. In this work, Haeckel used the term Stammzelle (“stem cell”) to describe the ancestor unicellular organism from which he presumed all multicellular organisms evolved. Particularly, he also suggested fertilized oocytes as the source giving rise to all cells of the whole body. In 1892, Valentin Hacker described stem cells as the cells that later produce oocytes in the gonads. Then, this term becomes more popular with some experimental results in developmental biology. Some studies about nuclear programming in the 1900s showed that adult cells can become pluripotent stem cells, and pluripotent stem cells can differentiate into all specialized cells from three germ layers. The first successful study about epigenetic reprogramming was performed by John Gurdon in 1962 in the African clawed toad, *Xenopus laevis*. He could produce healthy and sexually mature fertile frogs by nuclei transplantation from differentiated cells. Therefore, he and Shinya Yamanaka shared a Nobel Prize in Medicine or Physiology in 2012. Besides pluripotent stem cells, the multipotent stem cells also were detected and isolated in the adult, so-called adult stem cells. Adult stem cells such as hematopoietic stem cells and mesenchymal stem cells are the essential source of stem cells in an adult that play the important roles in tissue homeostasis, wound healing, and tissue regeneration after injuries. These discoveries suggested that stem cell transplantation can help to regenerate the injured tissues. And stem cell therapy, as well as regenerative medicine, was formed from these observations.

The first autologous stem cell transplant was undergone by Dr. E. Donnall Thomas in 1957; he later received the Nobel Prize in Medicine in 1990 for this achievement. The clinical application of hematopoietic stem cells rapidly grew from the 1990s to date. From the 2000s, some other adult stem cells including mesenchymal stem cells, limbal stem cells, epidermal stem cells, and neural stem cells were used in the clinic. In recent years, embryonic stem cells, as well as pluripotent stem cells (induced pluripotent stem cells), also were permitted for use in some clinical trials.

The clinical application of stem cells broke out since the 2000s when some countries approved some stem cell-based therapies and stem cell-based products. To date, stem cells including both adult stem cells and pluripotent stem cells were clinically used in more than 50 different diseases and medical conditions. More than ten stem cell-based therapies, as well as stem cell-based products, were approved as routine treatments in some countries.

Therefore, the *Stem Cells in Clinical Applications* series brings some of the field's most renowned scientists and clinicians together with emerging talents and disseminates their cutting-edge clinical research to help shape future therapies. While each book tends to focus on regenerative medicine for an individual organ or system (e.g., the liver, lung, and heart, the brain and spinal cord, etc.), each volume also deals with topics like the safety of stem cell transplantation, evidence for clinical applications including effects and side effects, guidelines for clinical stem cell manipulation, and much more. Volumes also discuss mesenchymal stem cell transplantation in autoimmune disease treatment, stem cell gene therapy in preclinical and clinical contexts, clinical use of stem cells in degenerative neurological disease, and best practices for manufacturers in stem cell production. Later volumes will be devoted to safety, ethics and regulations, stem cell banking, and treatment of cancer and genetic disease.

This volume, *Stem Cell Processing*, presents some significant sources of stem cells for clinical applications. Mainly, this volume also introduces some new techniques to collect and expand stem cells with GMP guidelines so that these obtained cells can be used in the clinic.

In the first edition of this volume, ten chapters will focus on the recent hot topic about some accepted and approved clinical applications of stem cells (Chapter One) and some clinical trials and approved products from mesenchymal stem cells (Chapter Two). The techniques for isolation and expansion of mesenchymal stem cells are also provided in Chapters Six, Seven and Ten. In this volume, some effects of aging and senescence on mesenchymal stem cell properties are also suggested in Chapters Three and Four. Some recent efforts in clinical usages of pluripotent stem cells are discussed in Chapter Four, with some concerns covered in Chapter Nine.

Many people have contributed to making our involvement in this project possible. We are extremely thankful to all of the contributors to this book. Many people have had a hand in the preparation of this book. We thank our readers, who have made our hours putting together this volume worthwhile. We are indebted to the staff of Springer Science+Business Media that published this book.

Ho Chi Minh City, Vietnam Phuc Van Pham

Contents

Contributors

Marco Alessandrini Department of Immunology, Faculty of Health Sciences, Institute for Cellular and Molecular Medicine, and SAMRC Extramural Unit for Stem Cell Research and Therapy, University of Pretoria, Pretoria, South Africa

W.M. Botes Dyason Inc. Firm of Attorneys, Pretoria, South Africa

Danielle de Villiers Department of Immunology, Faculty of Health Sciences, Institute for Cellular and Molecular Medicine and SAMRC Extramural Unit for Stem Cell Research and Therapy, University of Pretoria, Pretoria, South Africa

Carla Dessels Department of Immunology, Faculty of Health Sciences, Institute for Cellular and Molecular Medicine and SAMRC Extramural Unit for Stem Cell Research and Therapy, University of Pretoria, Pretoria, South Africa

Chrisna Durandt Department of Immunology, Faculty of Health Sciences, Institute for Cellular and Molecular Medicine and SAMRC Extramural Unit for Stem Cell Research and Therapy, University of Pretoria, Pretoria, South Africa

Emma Fossett University College London Institute for Orthopaedics and Musculoskeletal Sciences, Royal National Orthopaedic Hospital, Stanmore, UK

Danie Hoffmann Private Practice, Pretoria, South Africa

Deepak M. Kalaskar Centre for Nanotechnology and Tissue Engineering, UCL Division of Surgery and Interventional Science, London, UK

Karlien Kallmeyer Department of Immunology, Faculty of Health Sciences, Institute for Cellular and Molecular Medicine and SAMRC Extramural Unit for Stem Cell Research and Therapy, University of Pretoria, Pretoria, South Africa

Wasim S. Khan Division of Trauma & Orthopaedics, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK

University College London Institute for Orthopaedics and Musculoskeletal Sciences, Royal National Orthopaedic Hospital, Stanmore, UK

Juanita Mellet Department of Immunology, Faculty of Health Sciences, Institute for Cellular and Molecular Medicine and SAMRC Extramural Unit for Stem Cell Research and Therapy, University of Pretoria, Pretoria, South Africa

Ahmed K. Oloyo Department of Immunology, Faculty of Health Sciences, Institute for Cellular and Molecular Medicine and SAMRC Extramural Unit for Stem Cell Research and Therapy, University of Pretoria, Pretoria, South Africa

Yiannis Pengas Department of Trauma & Orthopaedics, Royal Cornwall Hospitals NHS Trust, Truro, Cornwall, UK

University College London Institute for Orthopaedics and Musculoskeletal Sciences, Royal National Orthopaedic Hospital, Stanmore, UK

Michael S. Pepper Department of Immunology, Faculty of Health Sciences, Institute for Cellular and Molecular Medicine, and SAMRC Extramural Unit for Stem Cell Research and Therapy, University of Pretoria, Pretoria, South Africa

Phuc Van Pham Laboratory of Stem Cell Research and Application, University of Science, Vietnam National University, Ho Chi Minh City, Vietnam

Biology-Biotechnology Faculty, University of Science, Vietnam National University, Ho Chi Minh City, Vietnam

Ngoc Kim Phan Laboratory of Stem Cell Research and Application, University of Science, Vietnam National University, Ho Chi Minh City, Vietnam

Biology-Biotechnology Faculty, University of Science, Vietnam National University, Ho Chi Minh City, Vietnam

Nhan Lu-Chinh Phan Laboratory of Stem Cell Research and Application, University of Science, Vietnam National University, Ho Chi Minh City, Vietnam

Marnie Potgieter Department of Immunology, Faculty of Health Sciences, Institute for Cellular and Molecular Medicine and SAMRC Extramural Unit for Stem Cell Research and Therapy, University of Pretoria, Pretoria, South Africa

Saiyyada Mohsina Shahid Centre for Nanotechnology and Tissue Engineering, UCL Division of Surgery and Interventional Science, London, UK

M. Nöthling Slabbert Department of Jurisprudence, School of Law, University of South Africa, Pretoria, South Africa

Helen C. Steel Department of Immunology, Faculty of Health Sciences, Institute for Cellular and Molecular Medicine and SAMRC Extramural Unit for Stem Cell Research and Therapy, University of Pretoria, Pretoria, South Africa

Hitesh D. Tailor University College London Institute of Orthopaedics and Musculoskeletal Sciences, Royal National Orthopaedic Hospital, Stanmore, UK

Nhung Hai Truong Laboratory of Stem Cell Research and Application, University of Science, Vietnam National University, Ho Chi Minh City, Vietnam

Biology-Biotechnology Faculty, University of Science, Vietnam National University, Ho Chi Minh City, Vietnam

Fiona A. van Vollenstee Department of Immunology, Faculty of Health Sciences, Institute for Cellular and Molecular Medicine and SAMRC Extramural Unit for Stem Cell Research and Therapy, University of Pretoria, Pretoria, South Africa

Ngoc Bich Vu Laboratory of Stem Cell Research and Application, University of Science, Vietnam National University, Ho Chi Minh City, Vietnam

About the Editor

Phuc Van Pham received his Ph.D. in human physiology from Vietnam National University, Ho Chi Minh City, Vietnam. He is currently a professor of biology at Vietnam National University and acting director of the Laboratory of Stem Cell Research and Application. He is a long-standing lecturer and translational scientist at the university and is a member of several societies and journal editorial boards focused on stem cells.

Dr. Pham and his colleagues have established one of the first multidisciplinary stem cell centers in Vietnam, and he has successfully launched an array of technologies in stem cell isolations. His research interests include stem cell isolation, stem cell therapy, mesenchymal stem cells, cancer stem cells, immunotherapy, and regenerative medicine, and he has published extensively in these areas.

After many years of experience as an embryologist, cell biologist, and molecular biologist, collaborating with leading researchers in Singapore, Japan, and the United States, Dr. Pham is a student again, keen to reach beyond the traditional boundaries of biology.

Chapter 1
Stem Cell Therapy: Accepted Therapies, Managing the Hope of Society, and a Legal Perspective

W.M. Botes, M. Nöthling Slabbert, M. Alessandrini, and M.S. Pepper

1.1 Background

There is little doubt that stem cells hold great promise for the treatment and cure of many diseases. Along with this promise however comes great expectation, which should be managed cautiously if the true potential of the stem cell research is to be realized. Several misconceptions persist in society in general and to an extent among the medical fraternity. These misconceptions, coupled to irresponsible clinical practices, have resulted in exploitation of vulnerable patients. Guidelines and legislation are being developed globally with the aim of providing ethically sound reference material for patients, practitioners, and regulators. However, as with most developing frameworks, a lack of regulatory cohesiveness often results. An overview of the current global regulatory framework is provided, including anticipated legal developments and recommendations.

W.M. Botes
Dyason Inc. Firm of Attorneys, Pretoria, South Africa

M. Nöthling Slabbert
Department of Jurisprudence, School of Law, University of South Africa, Pretoria, South Africa

M. Alessandrini • M.S. Pepper (✉)
Department of Immunology, Faculty of Health Sciences, Institute for Cellular and Molecular Medicine, and SAMRC Extramural Unit for Stem Cell Research and Therapy, University of Pretoria, Pretoria, South Africa
e-mail: michael.pepper@up.ac.za

P.V. Pham (ed.), *Stem Cell Processing*, Stem Cells in Clinical Applications,
DOI 10.1007/978-3-319-40073-0_1

1.1.1 Basic Principles of Stem Cell Biology

A stem cell has the unique ability to differentiate into the various cell types of the body, while simultaneously replicating to maintain a stem cell lineage. Different forms of stem cells exist, each with varying capacity or potency. Potency refers to the ability of a stem cell to replicate and differentiate into different cell types. When the female egg cell is fertilized by the male sperm, a zygote is created. The zygote is referred to as a totipotent stem cell, which by definition has the potential to develop into the entire human body, including the placental tissues required for the early developmental stages of the embryo and fetus. After several cycles of replication, the zygote develops into a blastocyst, which consists of an outer layer of cells and an inner cell mass. The outer layer develops into tissues of the placenta, while the inner cell mass develops into the embryo. Embryonic stem cells (ESCs) are derived from the inner cell mass and are referred to as pluripotent stem cells. These cells have the ability to form any cell type of the human body, with the exception of cells of the placenta. Adult stem cells are multipotent and are present in various adult tissues and organs. They possess a renewal and regenerative capacity which is generally limited to the tissue within which they reside. The best known examples of multipotent stem cells are (1) hematopoietic stem cells (HSCs), which give rise to all of the cellular components of the blood; (2) mesenchymal stem cells (MSCs), which are able to develop into the bone, cartilage, muscle, and fat; and (3) neural stem cells (NSCs), which develop into cells of the nervous system. There is a large research community investigating the biology and therapeutic potential of stem cells. However, with the exception of HSC transplantation, the clinical benefit of stem cell therapies is yet to be demonstrated.

1.1.2 Clinical Applications of Stem Cell Therapy

The only globally accepted form of stem cell therapy is the use of HSCs for transplantation purposes—a practice that is successfully being applied in nearly 80 countries around the world. Of the more than 60,000 HSC transplants that take place globally per annum, the vast majority (>80 %) are for treating hematological malignancies, namely, acute and chronic leukemia, both Hodgkin's and non-Hodgkin's lymphoma, and the plasma cell disorders (mostly multiple myeloma). Secondary to these indications is the treatment of solid tumors, while nonmalignant conditions include bone marrow failures, hemoglobinopathies, and primary immune disorders. In all cases, the HSCs are used to replenish blood cells that are depleted in a chemotherapy regimen administered prior to the transplantation. In addition to these indications, there is a movement toward using HSCs for regenerative purposes, such as for treating cerebral palsy, autism, and type I diabetes. These approaches are still experimental, and sufficient evidence for their routine use is yet to be provided.

The potential benefit of using MSCs to treat a variety of conditions has gained significant interest in recent times. The primary reasons for this trend include the fact that these cells (1) can easily be procured from sources such as the bone marrow, umbilical cord blood, and adipose tissue; (2) have the unique ability to home to the site of injury once administered; and (3) do not require genetic matching when obtained from a donor (as is the case with HSCs). A large number of indications are being treated with MSCs at present, and based on our investigations of the clinical trial landscape, it is possible to cite over 120 different indications that have been treated in this setting. These include cardiovascular diseases such as myocardial infarction, cardiomyopathy and heart failure, neurological disorders such as multiple sclerosis and amyotrophic lateral sclerosis, and musculoskeletal conditions such as fracture non-unions and cartilage defects. To date however, only one MSC product has successfully achieved market approval from regulatory authorities, namely, Prochymal (developed by Osiris Therapeutics and acquired by Mesoblast Ltd. in Australia), which was approved in Canada and New Zealand for the treatment of graft versus host disease, a complication of HSC transplantation.

1.2 Controversies and the Consequence of Providing Unproven Stem Cell Therapies

The stem cell controversies of the past two decades have originated from the use of ESCs for medical research. Given that a fertilized embryo is destroyed in order to derive these cells, albeit in the laboratory setting with donated embryos, such research is deemed unacceptable by many and understandably has resulted in ethical debate. More recently, however, the use of unproven stem cell therapies and the subsequent emergence of a "stem cell tourism" industry have become a controversial issue in its own right. In such cases, vulnerable patients are enticed to travel abroad to dubious stem cell clinics and are subjected to unproven stem cell therapies at their own expense. Given the unique properties of MSCs and the ease with which they can be prepared from fat tissue, they have become the most attractive product/service on offer at a large number of so-called stem cell clinics around the world. The most concerning aspect is the extensive list of diseases that these clinics claim to treat. Although over 100 indications are being treated in the clinical trial setting, clinical benefit has been demonstrated in very few (with the exception of the previously mentioned Prochymal preparation).

1.2.1 Reference to Pertinent Issues and Controversial Reports

Clinics offering many different kinds of stem cell treatments for a wide range of diseases and conditions available for direct purchase through online market places have been established around the world, not only in developed countries such as the

USA and various European countries but also in newly industrialized countries such as China, India, and Mexico (Lau et al. 2008). While it was thought that the majority of clinical trials involving stem cells take place in the USA, the majority of trials involving MSCs currently take place in East Asia and Europe (Clinicaltrials.gov 2015), but the official number of these trials may be skewed as a result of underreporting. It should further be noted that the entry of any clinical trial information into a register does not imply endorsement of the trial by the regulatory authority in the country or region in which the trial is taking place.

With increasing global stem cell activity, further increases in offers for stem cell treatments are inevitable, and with different regulatory regimes in each country, the marketing, administration of stem cell treatments, and general management of society's hope are causes for concern (Caulfield et al. 2012). Even though the fact that potentially fraudulent treatments are being offered for a large number of conditions and that this is receiving increased attention, marketing practices not only remain unchanged but claims have actually escalated (Ogbogu et al. 2013). This situation leads increasingly to so-called scienceploitation and stem cell tourism where evidence suggests that the majority of people, desperate after finding out that conventional medicine offers no available treatment, travel mostly from developed countries to developing countries with no, poor, or more liberal regulations regarding stem cells, in an effort to access stem cell treatments (Regenberg et al. 2009). Major destinations are China, India, Mexico, Germany, and the Dominican Republic, which primarily treat conditions such as blindness, paralysis, multiple sclerosis, cerebral palsy, and brain injuries (Levine and Wolf 2012). Most of these treatments are still unproven and unauthorized, lacking testing of efficacy and safety, and thus pose a threat to people's lives, health, and emotional and financial well-being.

Stem cell tourists spent an average of $20,000–$50,000, travel expenses excluded, on clinically unproven treatments in 2014 (IOM and NAS 2014). Some received stem cells from animals such as sheep or rabbits, and stem cells were injected subcutaneously, intramuscularly, intravenously, via lumbar puncture, or into the subdural space during spinal surgery (Pepper 2009). Complications involving stem cell treatments include tumor growth (Amariglio et al. 2009), multiple autoimmune diseases (Bohgaki et al. 2007), meningitis (Mendpara et al. 2002), angiomyeloproliferative lesions (Thirabanjasak et al. 2010), and bone fragments growing in a patient's eye after cosmetic surgery (Jabr 2012).

From 2002 until 2006, Biomark International defrauded individuals suffering from amyotrophic lateral sclerosis (Lou Gehrig's disease), Parkinson's disease, muscular dystrophy, multiple sclerosis, and other incurable diseases by making false representations "…that science had proven the therapeutic power of stem cells and that Biomark was simply making it available to the world." (*United States of America v. Laura Brown and Stephen Mark van Rooyen* 2006). Under these pretenses, every patient was injected with the same type and quantity of stem cells, regardless of the disease they were suffering from, and charged between $10,000.00 and $32,000.00, if not negotiated otherwise. In 2006 Laura Brown and Stephen Mark van Rooyen, the directors of Biomark, were criminally indicted. During their hearing, the court also found that Biomark's website and advertisements made

numerous false, misleading, and inaccurate statements and that the proffered information had no scientific credibility. It further found that the stem cell treatments were illegally administered without a biologics product license (Public Health Services Act, Section 262(a)(1) 2011) and that licensing was very unlikely as preclinical trials in this regard only involved nonhumans. None of the patients undergoing these treatments were cured and many even died during the course thereof (Mahomed and Nöthling Slabbert 2012).

Medical tourism in this context can broadly be divided into three categories (IOM and NAS 2014):

1.2.1.1 According to the Legal Status of the Treatment

Some treatments are illegal in the patient's home country but legal in the destination country, a medical tourism style known as *circumvention tourism*, which includes abortion, assisted suicide, and stem cell treatments. Sometimes stem cell treatments might not necessarily be illegal in a patient's home country, but simply unavailable due to the fact that they are not yet approved.

1.2.1.2 According to Who Is Paying for the Treatment

In some cases, patients are paying from their own funds, but increasingly large insurers in the USA and Australia pay for medical tourism packages to nationals who are looking for lower-cost options elsewhere in clinics with guaranteed safety and quality (Parnel 2013). However, insurers in the USA typically refuse payment for experimental or investigational treatments unless clinical safety and effectiveness have been proven.

1.2.1.3 According to Where Patients Are Traveling for Treatment

Patients may travel from one developed country to another developed country, from a developed country to a less developed country, or from a less developed country to a more developed country.

However, progressing from basic research to clinical research to eventual translation thereof is a long, laborious, and expensive process with an increase in the number of patients at every successive stage, which means a similar increase in costs and risks. However, the majority of stem cell clinical trials are in the early stages, enrolling only a small number of patients (Trouson et al. 2011). The translation of stem cell therapy will only be safely and effectively achieved through international collaboration, including the sharing of research information to improve global public health. Advances in science and technology will facilitate the development of safe and effective biological products, thereby advancing regulatory science and research and managing organizational excellence and accountability (CBER 2011).

Considering the global fluency of patients seeking stem cell treatments in countries with differing regulatory regimes, ethical beliefs, and societal values, it is important to consider the ethical, legal, and social issues which inform these regulatory frameworks and policies.

1.2.2 Ethical and Legal Concerns

The main ethical issues in somatic stem cell research concern the sources and sourcing of stem cells, moral status of the human embryo, informed consent, reproductive as opposed to therapeutic cloning, and the clinical use of stem cells.

1.2.2.1 Sources and Sourcing of Human Stem Cells

Although stem cells are usually sourced from noncontroversial sources such as the bone marrow, umbilical cord blood, and adipose tissue, to which the below-discussed ethical and legal issues do not necessarily apply, this section will specifically deal with the controversial sources producing ethical and legal debate.

Human ESCs are mainly sourced from embryos arising from infertility treatment cycles, embryos created specifically for research purposes, somatic cell nuclear transfer (SCNT), and cadaveric fetal tissue.

hESCs are derived from the inner cell mass of a human blastocyst which is formed 5–7 days after fertilization. The inner cell mass of the blastocyst is destined to become all of the tissues of a human body after the trophoblast of the blastocyst becomes placental tissue upon successful implantation (Patil 2014). The destruction of the human embryo during extraction of hESCs is therefore inevitable and therefore the source of much ethical and legal debate regarding the moral status and legal personhood of the embryo.

Moral and Legal Status of an Embryo

At the one end of the spectrum is the belief that an embryo is created by God from the moment of conception and from then constitutes a person with the same moral rights as any adult human (Doerflinger 1999), while alternative views share the belief that the embryo acquires complete personhood and its accompanying rights in gradual stages during the process of development from conception to birth (House of Lords Select Committee on Science and Technology 2002). The latter view has found general social, ethical, and legal favor. At around 14 days after fertilization, the primitive streak of an embryo is formed when a thickening of the surface, indicating the first organization of the embryo, takes place. This has been suggested as a key cutoff point after which research involving embryos is prohibited. Up to 14 days the blastocyst has no central nervous system, a further landmark for the

definition of life, since a nervous system implies the possibility of sensation (Fishbach and Fishbach 2004). The early embryo up to this point was termed the "pre-embryo" in 1985, and notwithstanding arguments that this term was merely invented to justify embryonic research, the 14-day limit has generally been accepted and adopted in various jurisdictions globally (Mulkay 1997).

Although the Universal Declaration of Human Rights (UDHR) stipulates that all human beings are born free and equal in dignity and rights (UDHR, Article 2), the term "born" was used to exclude the fetus and embryo from the human rights granted in this declaration. Arguments to amend the UDHR by deleting this term were proposed but rejected (Copelan et al. 2005). Even the Convention on the Rights of the Child (CRC, Article 6) only recognizes the right to life from birth (Copelan et al. 2005). Although the US Supreme Court has never ruled on the constitutional status of human embryos outside the body, it has ruled that fetuses are not persons within the meaning of the 14th Amendment and accordingly have no constitutional rights (Robertson 2010). This ruling will presumably also extend to embryos, but although the American Convention on Human Rights (ACHR 1969, Article 4) stipulates that every person's right to life must be respected, that this right must be protected from the moment of conception, and that no one shall be arbitrarily deprived of his life, the Inter-American Commission on Human Rights clarified that this right is not absolute (Center for Reproductive Rights undated). In the matter of *Paton v United Kingdom* (1980), the European Commission on Human Rights held that the language of Article 2(1) of the European Convention on Human Rights (ECHR) which provides that "Everyone's right to life shall be protected by law" (ECHR Article 2) does not include the unborn and acknowledged that the recognition of an absolute right to life before birth would be contrary to the object and purpose of the said convention. In *Vo v France* (2004), the European Court of Human Rights affirmed that the unborn child is not regarded as a "person" directly protected by Article 2 of the ECHR and that if the unborn child does have a right to life, such right is implicitly limited by the mother's rights and interests. However, these cases refer specifically to unborn children in utero as opposed to embryos outside the human body (*Roe v Wade* 1973; *Planned Parenthood v Casey* 1992).

However, on 18 December 2014 in the patent matter of *International Stem Cell Corporation v Comptroller General of Patents, Designs and Trade Marks* (2013), the Court of Justice of the European Union ruled that embryos created through parthenogenesis, being unable to develop into human beings and having only one set of DNA, do not qualify as a human embryo having regard to the definition thereof contained in the European Parliament and Council's Directive 98/44/EC (1999) regarding the legal protection of biotechnological inventions dated 6 July 1999, and were therefore patent eligible.

The debate about the moral status of the embryo is not regarded as an ethical or legal one only. There is an obligation to do everything possible to alleviate the suffering of existing human beings, and if hESC research is the method to such a means, there is a moral duty to pursue it (Nuffield Council on Bioethics 2000).

Embryos Arising from Infertility Treatment

Although an embryo created for a reproductive technology program has been created with the view to implantation in the uterus and a successful pregnancy, it has no further use or future if it is not implanted. Rather than being discarded, spare embryos can be donated and used to derive stem cells (Thompson 1995). In most jurisdictions it is illegal to incentivize embryo donations and for the donors to have any financial stake in any materials or procedures developed from such donation (Corrigan et al. 2006). The commercialization of embryos as well as cadaveric fetal tissues are also banned (European Group on Ethics in Science and New Technologies to the European Commission 2002). The opinion has also been held that with the establishment of immortal cell lines, the need for further embryos by means of donation may become unnecessary and that the ethical questions surrounding issues in this regard may only be "transitional" until such time as a sufficient supply of stem cells from such lines can be secured (Nuffield Council on Bioethics 2000).

Embryos Created Specifically for Research Purposes

Embryos found unsuitable for IVF and donated after completion of a reproductive technology program will routinely be discarded, and the view exists that the derivation of ESC from such embryos will thus not affect their final disposition. But embryos created through in vitro fertilization (IVF) with the sole purpose to produce cell lines are essentially treated as a means to an end, and this does not accord with the respect owed to a potential human life. However, schedule 2 of the UK's Human Fertilization and Embryology Act (HFEA 1990) permits the creation of embryos for the specific research purposes as set out therein if a research project cannot be carried out on donated embryos. This situation is kept under review in the UK as the opinion exists that while there are sufficient donated embryos from IVF treatments, there are no compelling reasons to allow the creation of additional embryos merely for the sake of increasing the number of embryos available for research purposes (Nuffield Council on Bioethics 2000). The Council on Human Rights and Biomedicine, on the other hand, prohibits the creation of human embryos for research purposes, but not hESC research based on supernumerary or excess IVF embryos (Council of Europe 1997). Embryos created deliberately for research purposes remain a contested issue, and this is also closely linked to funding regulations for stem cell research.

Sourcing of Oocytes for the Creation of Embryos

Donation of oocytes involves hyperstimulation of the ovaries by hormone injection followed by surgery to harvest the produced oocytes. This process is painful and carries significant risks. Donation of oocytes to help infertile couples is considered to be an altruistic gesture, and money paid in this regard is seen as compensation for

the inconvenience, discomfort, or incurred expenses relating to the donation, not as payment for the oocytes. It is interesting to note that the Human Fertilization and Embryology Authority now allows limited compensation to oocyte donors in respect of lost earnings (Human Fertilization and Embryology Authority 2005).

In February 2004, Dr Hwang Woo-suk and his South Korean colleagues reported on their successful cloning of 30 human embryos from which they extracted stem cell lines (Hwang et al. 2004). In May 2005 Dr Hwang and his colleagues announced that they managed to make 11 patient-specific cell lines by using donated eggs and DNA from people suffering from diabetes and spinal cord injuries (Hwang et al. 2005). Not only did these papers contain fraudulent data, necessitating the authors to retract the articles, but the sourcing of oocytes for research purposes also raised serious ethical concerns (Normile et al. 2006; Kennedy 2006). It transpired that many of the oocyte donors suffered hyperstimulation syndrome resulting from donation (Chong 2006) and that some of the eggs were donated by junior female researchers that were part of the research team, pointing to possible coercion by senior investigators in the same team (Normile et al. 2006). This incident again raised issues of informed consent and compensation for oocyte donation.

A suggested alternative solution to the shortage of ova and the potential ethical problems involving donation is to use ova from other species in the creation of stem cells by means of nuclear replacement (Holm 2002). This technique for the creation of so-called hybrids or chimeras, organisms with a mixture of cells from two or more genetically distinct species, has been patented by the American firm Advanced Cell Technology (1998), but has been received with skepticism (Marshall 1998). One of the main arguments in favor of the creation of chimeras or hybrids is that many necessary stem cell experiments are ethically and legally prohibited from being performed on humans. Experiments involving chimeras or hybrids are subject to ethical and legal guidelines involving the use of animals in research activities (Knowles 2010).

Cadaveric Fetal Tissue

The acceptability of using fetal tissue to derive embryonic germ cells (EGC) is closely tied to the ethical acceptability of abortion. Pluripotent cells, derived from the blastocyst, have the potential to develop into any of these cell types in the body. Because these cells are derived from the embryo, they are called embryonic stem cells (ESCs). If these cells are derived from the region destined to develop into sperm and eggs, known as primordial germ cells in the fetus, they are called EGCs. Although attempts to derive adult cells from EGCs in mice have led to abnormalities and research is currently focused on ESCs, the Polkinghorne Review suggested that consent for the use of donated fetal tissue for the purpose of deriving EGC be reconsidered (Nuffield Council in Bioethics 2000).

A major concern is that abortions would then be sought with the primary objective of donating cadaveric fetal tissue in return for possible therapeutic of financial