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**Do Induced Pluripotent Stem Cells Resolve the Ethical and Legal Issues
Generated by Human Embryonic Stem Cells?**

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RCSI

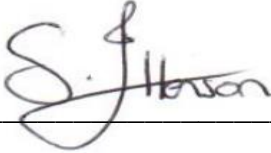
**A dissertation submitted in partial fulfilment of the requirement for
the Masters in Healthcare Ethics and Law**

Supervisor: Ms Gina Menzies

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Declaration

I declare that this thesis, which I submit to RCSI for examination in consideration of the award of a higher degree, MSc in Healthcare Ethics and Law, is my own personal effort. Where any of the content presented is the result of input or data from a related collaborative research programme this is duly acknowledged in the text such that it is possible to ascertain how much of the work is my own. I have not already obtained a degree in RCSI or elsewhere on the basis of this work. Furthermore, I took reasonable care to ensure that the work is original, and, to the best of my knowledge, does not breach copyright law, and has not been taken from other sources except where such work has been cited and acknowledged within the text.

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Abbreviations

ANT	Altered Nuclear Transfer
DNA	Deoxyribonucleic acid
EPO	European Patent Office
EU	European Union
HeLa	HeLa cells were the first human cells to be continuously grown in culture. They were named after the donor of the original cells, Henrietta Lacks.
HFEA	Human Fertilisation and Embryology Authority (UK)
HLA	The 'Human Leukocyte Antigen' system which is the locus of genes that encode for proteins on the surface of cells that are responsible for regulation of the immune system in human.
IVF	In Vitro Fertilization
NIH	National Institutes of Health (USA)
PGD	Pre-Genetic Diagnosis
RNA	Ribonucleic acid
SCNT	Somatic Cell Nuclear Transfer
UK	United Kingdom
USA/US	United States of America

Glossary of terms

Adenoviral Vector	Any of a large group of viruses causing disease of the upper respiratory tract and conjunctiva, and also present in latent infections in normal persons; used to used to insert sequences into an organism's cells.
Adult Stem Cells	Adult stem cells are undifferentiated cells found throughout the body that divide to replenish dying cells and regenerate damaged tissues.
Antigen	A toxin or other foreign substance which induces an immune response in the body, especially the production of antibodies.
Autonomy	The right or condition of self-government.
Blastocyst	Over the course of day five of development, the Morula begins to hollow out and fill with fluid. These additional characteristics transform it into what is known as the Blastocyst.
Canavan Disease	A progressive, fatal neurological disorder that begins in infancy. It is caused by an inherited genetic abnormality: the lack of an essential enzyme causes deterioration of the white matter (myelin) in the brain, thereby preventing the proper transmission of nerve signals.
Cell Differentiation	A biological process through which every cell, whether the liver, heart, or brain, takes on its role by specialising into a particular cell type, with a characteristic shape and function.

Cell de-differentiation	The regression of a cell from a more specialized state back to a simpler state that confers pluripotency, giving rise to cells reminiscent of stem cells.
Chromosomes	A thread-like structure of nucleic acids and protein found in the nucleus of most living cells, carrying genetic information in the form of genes.
Cognitive	Of or relating to the mental processes, e.g. memory, judgement etc.
Conception	The moment when a sperm cell breaches the ovum, or egg.
Consequentialism	An ethical theory that human actions derive their moral worth solely from their outcomes or consequences.
Culture Dish	A shallow circular dish with a loose-fitting cover, used to culture bacteria or other microorganisms.
Cryopreservation	Is a process where cells, whole tissues, or any other substances susceptible to damage caused by chemical reactivity or time are preserved by cooling to sub-zero temperatures.
Cytoplasm	The material or protoplasm within a living cell, excluding the nucleus.
Deontology	An ethical theory that the morality of an action should be based on whether that action itself is right or wrong under a series of rules, rather than based on the consequences of the action.

Embryogenesis	Period of time which spans from the end of fertilisation (zygote stage) until the end of the eighth week of development, after which the developing human is referred to as a foetus.
Embryonic Stem Cells	Stem cells which originate from an embryo. These cells are formed and extracted within the first four to five days after fertilization has occurred.
Empirical	Relying on or derived from observation or experiment.
Ensoulement	The point at which the soul is believed to enter the human body.
Enucleated Cell	A cell which no longer contains its nucleus.
Epigenetic	Relating to or arising from non-genetic influences on gene expression.
Epithelial	The thin, membranous tissue that lines most of the internal and external surfaces of an animal's body.
<i>Fard Kifaya</i>	Islamic term used to describe a collective religious obligation.
Fertilization	The process whereby two sex cells (an ovum and a sperm) fuse together to become a zygote.
Fibroblast	A cell in connective tissue which produces collagen and other fibres.
Foetal Stem Cells	These kinds of stem cells are derived from the tissue of aborted fetuses within the time frame of five to nine weeks post-fertilization.
<i>Foetus Animatus</i>	A Christian term used to refer to an embryo which had acquired a soul; literally translated as an animated embryo.

<i>Foetus Inanimatus</i>	A Christian term used to denote an embryo before it acquired a soul; literally translated as an inanimate embryo.
Gastrula	Two weeks after fertilization, the cells of the inner cell mass of the blastocyst begin to form into distinct cell types which will form the embryo; it is now referred to as a Gastrula.
<i>Hadith</i>	An Islamic book of the sayings and actions of the Prophet Muhammad.
<i>Ijtihad</i>	Islamic term used to describe independent judgement.
Implantation	The point when the fertilized blastocyst attaches to the lining of the uterus/womb.
Induced Pluripotent Stem cells	Stem Cells which have been created through the application of transcription factors to a somatic cell.
<i>In utero</i>	Cultivated or developed within a womb.
<i>In vitro</i>	Cultivated or developed within a laboratory; usually within a culture dish and/or test tube.
Inner Cell Mass (ICM)	Consists of the mass of cells inside the early embryo that will eventually give rise to the definitive structures of the foetus.
Lentoviral Vector	An artificial construct which can deliver a significant amount of viral RNA into the DNA of the host cell and have the unique ability among retroviruses of being able to infect non-dividing cells.
Mitochondria	An organelle found in large numbers in most cells, in which the biochemical processes of respiration and energy production occur.

Mitosis	A type of cell division that results in two daughter cells each having the same number and kind of chromosomes as the parent nucleus, typical of ordinary tissue growth.
Moral Status	A characteristic that we human moral agents attribute to entities, by virtue of which they matter morally for their own sake, so that we must pay attention to their interests or integrity when we consider actions that might affect them, regardless of whether other beings are concerned about them.
Morula	By dividing four or five times since fertilization, the formation of a solid ball of 16-32 cells called the Morula is formed.
Multipotent Stem Cells	Multipotent stem cells refer to the group of stem cells which can give rise to a limited number of specialised cells within the body but only those of a closely related family of cells.
Oocyte	An immature female sex cell, which after two cell divisions becomes an ovum. Contains 23 chromosomes.
Patent	A government authority or license conferring a right or title for a set period, especially the sole right to exclude others from making, using, or selling an invention.
Personhood	The quality or condition of being an individual person.
Pluripotent Stem Cells	This category of stem cells can indefinitely produce specialised cells for any part of the body.
Pre-embryo	This term was employed in order to differentiate between an early embryo of up to 14 days of age since fertilisation, and one of later development.

Primitive Streak	The faint streak which is the earliest trace of the embryo in the fertilized ovum of a higher vertebrate.
<i>Qur'an</i>	The Islamic book of faith.
Retroviral Vector	An artificial DNA construct derived from a retrovirus, used to insert sequences into an organism's chromosomes.
Somatic Cell	Any cell of a living organism other than the reproductive cells.
Sperm	Male sex cell. Contains 23 chromosomes.
Stem Cell Line	Refers to stem cells which have been isolated from an organism and transferred to an <i>in vitro</i> culture within a laboratory, whereby the stem cells multiply indefinitely.
Supernumerary	Present in excess of the normal or requisite number.
Surrogate	A substitute; especially a person deputizing for another in a specific role or office.
Totipotent Stem Cells	These are stem cells which possess the ability to differentiate into all the different kinds of cells within the human body, and so are able to give rise to an entire organism.
Transcription Factor	Proteins involved in the process of converting, or transcribing, DNA into RNA. These factors initiate and regulate the transcription of genes.
Transgene	A transgene is a gene or genetic material that has been transferred naturally, or by any of a number of genetic engineering techniques from one organism to another.

Utilitarian	A branch of Consequentialism; the doctrine that actions are right if they are useful or for the benefit of a majority.
Viral Vector	Viral vectors are tools commonly used by molecular biologists to deliver genetic material into cells.
Zygote	The product of fertilization – one cell containing all 46 chromosomes.

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Abstract

The field of stem cell technology has seen an exponential growth over the last decade. Due to this, little attention has been paid as to whether this new technology adequately improves on previous research models, or indeed if it causes any ethical or legal issues itself. Of particular interest is whether Induced Pluripotent Stem Cells resolve the ethical and legal issues which have been generated by Human Embryonic Stem Cells. The ethical issues of note relate to the definition of personhood and moral status, the debate on when these can be ascribed, the consequences of utilising embryos for research, and whether the new method of inducing pluripotency stimulates any ethical issues itself. The central legal issues revolve around the diverse regulations which guide current research around the world, legal definitions regarding a child's right to life, whether such a right exists, the scope of consent, the limits of confidentiality, as well as whether current patent guidelines adequately stimulate research into this important area of medical development. The expected outcome of this exploration is that where induced pluripotency may appear to alleviate most of the ethical issues raised by human embryonic stem cells, the same may not be affirmed to a similar extent in the legal sphere, rather it is suggested that the employment of this new alternative method of creating stem cells may complicate the legal matters further. It is recommended that further investigation to harmonizing legal definitions as well as updating current regulations occurs, in order to avoid the exploitation of potentially vulnerable groups of the population.

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Thank you all.

1. Introduction

“Stem cell research can revolutionise medicine, more than anything since antibiotics.”

-Ron Reagan(1)

What if someone told you that you could potentially live forever? That you'd never die from a degenerative disease or otherwise? What if the science exists and all we're waiting for is a breakthrough?

Human stem cell research has made astonishing progress since the discovery of embryonic stem cells in 1998. While stem cell research has given hope to those who suffer from degenerative and neurological disorders such as Alzheimer's or Parkinson's Disease, ethical and legal issues related to human embryonic stem cells have tainted the popular appeal of this important medical research, in some countries causing severe research restrictions or a complete ban on pursuing such medical exploration.

This ethical and legal backlash is focused on the consequences to an embryo when it is used as a means to obtain human embryonic stem cells, namely its destruction. An overview of the method and consequences of accessing and collecting human embryonic stem cells will lay the foundation for the remainder of the thesis. Understanding the moral aversion to human embryonic stem cell research as well as the ethical and social issues which this research stimulates, will help the reader fully understand and appreciate the necessity of establishing an alternative method of obtaining human stem cells. The most recent method, which has been hailed as the moral and ethical alternative, which is focused on in this examination is that of inducing pluripotency within human adult somatic cells i.e. induced pluripotent stem cells.

The aim of this thesis is to establish if this new alternative method of inducing pluripotency within adult somatic cells adequately addresses or resolves the ethical and legal issues created by the research and use of human embryonic stem cells.

This analysis will firstly explore the background of stem cell research in its entirety; focusing on what stem cells are, the difference between certain kinds of stem cells, where these cells can be found, and their potential applications in medicine. The discourse will then go into more detail concerning human embryonic stem cells and the specific information concerning the methods through which these may be obtained. After this, the methods and implications of induced pluripotent stem cells will be explored, focusing on the development of this new approach, the different methods which can create these cells, and if any problems currently exist with this alternative method.

To conclude whether or not induced Pluripotent Stem Cell research alleviates the ethical and legal issues stimulated by human embryonic stem cell research, a detailed exploration of the issues is essential.

The ethical issues of human embryonic stem cells explored in this thesis comprise of the diverse understandings of the beginning of life and its connection to personhood, the differing religious perspectives which impact this understanding, the interpretation and application of language employed within the start of life debate, the potential of an unborn embryo, the social issues of utilising alternative sources of human embryonic stem cells which have been noted as possibly commercialising the human body as well as prompting the unethical creation of intentionally maimed embryos.

These ethical issues will then receive comparative analysis with the alternative method of inducing pluripotency in adult somatic cells. Specifically, each ethical issue will be addressed in the context of induced pluripotent stem cells as a viable alternative to human embryonic stem cells. It is suggested that through this analysis it may become apparent that induced pluripotent stem cells obviate or resolve many of the ethical issues generated through human embryonic stem cell research. As well as this, the method of inducing pluripotency may stimulate its own ethical concerns, such as unwanted outcomes and issues of justice, which will also receive further elucidation.

Consequently, the present legal context governing stem cell research, collection and storage will be examined as well as the implications these regulations have on the progress of this significant area of medical research within certain leading countries in the field, for example the UK and the US.

Within this context, the problems created by legal definitions and the right to life will be examined, as well as the important legal parameters of consent and confidentiality, and lastly, the area of patenting stem cells.

These issues will be comparatively critiqued against the background of induced pluripotent stem cells as a viable alternative to human embryonic stem cells. It is believed that where induced pluripotency may appear to alleviate most of the ethical issues raised by human embryonic stem cells, the same may not be affirmed to a similar extent in the legal sphere. It is suggested that the employment of this new alternative method of creating stem cells may complicate the legal matters further; from the outset it appears uncertain as to whether the method of inducing pluripotency adequately resolves the legal issues caused by human embryonic stem cell research.

However, the hopes and potential benefits of this medical technology are seen as being too great to ignore. If there is a possibility that an alternative, more ethically and legally moral, method of creating stem cells exists, is it not a duty for medical researchers to abandon traditional methods and employ the newer alternative? Before this can be answered, the primary question of this thesis needs to be thoroughly explored:

Do Induced Pluripotent Stem Cells resolve the ethical and legal issues generated by Human Embryonic Stem Cells?

2. What are Stems Cells?

There is little public understanding of the origin and potential of stem cells (2). This chapter will be outlining the discovery, research, classification, biological and scientific origins, applications, and possibilities of stem cells and stem cell research. Only once this basic foundation has been laid will a robust debate concerning the ethical, legal and even scientific issues of stem cells be possible.

The initial proposition that stem cells existed remained "largely hypothetical until research on survivors of the 1945 nuclear bombings was carried out and the term re-emerged to describe cellular regeneration mechanisms found to exist throughout the body" (3). This discovery was made through the assessment that even though red blood cells typically have a life span of four months, the human body continued to generate fresh blood cells to replace the ones lost. "This regeneration is guaranteed by stem cells residing in bone marrow, which can differentiate into any one of the various types of blood cells" (3). Such cellular regeneration mechanisms were further explored and it was found that a particular type of special cell - a stem cell - was capable of regenerating not only red blood cells, but other types of specialised cells. The main focus then turned to exploring the biological make up of stem cells and their locations in the human body.

A vast amount of research has been focused on pinpointing the capacities of stem cells - where they originate, how they maintain their potency, their ability to seemingly divide indefinitely and more

Stem cells have been described as a class of undifferentiated cells of a multi-cellular organism which have the potential to give rise to indefinitely more cells of the same type. From the initial (stem) cells, other more complex kinds of cells begin to form through a process known as *cell differentiation*. Cell differentiation is a biological process through which "every cell, whether the liver, heart, or brain, takes on its role by specialising into a particular cell type, with a characteristic shape and function" (3). The most important aspect of stem cells is that these are the **only cells** in multi-cellular organisms which have the capability to differentiate into many, if not **any**, cell types.

Thus the two crucial attributes of stem cells are:

1. Their **ability to proliferate** as well as
2. Their **potential to differentiate** (4)

While all stem cells share these attributes, it has been found that not all stem cells possess the same capacity or potency to proliferate and differentiate.

2.1 The Different Kinds of Stem Cells

Closely linked to the regeneration and production of new cells, is the type of stem cell which is producing the new cells. While each kind of stem cell possesses the ability to produce specialised cells, in most types the differentiation which is possible is quite limited. The three main categories of stem cells have been defined based on their ability to differentiate and can be described as follows:

1. Totipotent Stem Cells

These are stem cells which possess the ability to differentiate into **all the different kinds of cells** within the human body, and so are able to give rise to an entire organism. These would be the same cells from which embryos develop; they are produced during the process of fertilization and embryogenesis.

2. Pluripotent Stem Cells

This category of stem cells, while not able to regenerate or produce an entire organism, can indefinitely produce specialised cells for **any part of the body**. This category of stem cells originate as the inner cell mass within a blastocyst.

3. Multipotent Stem Cells

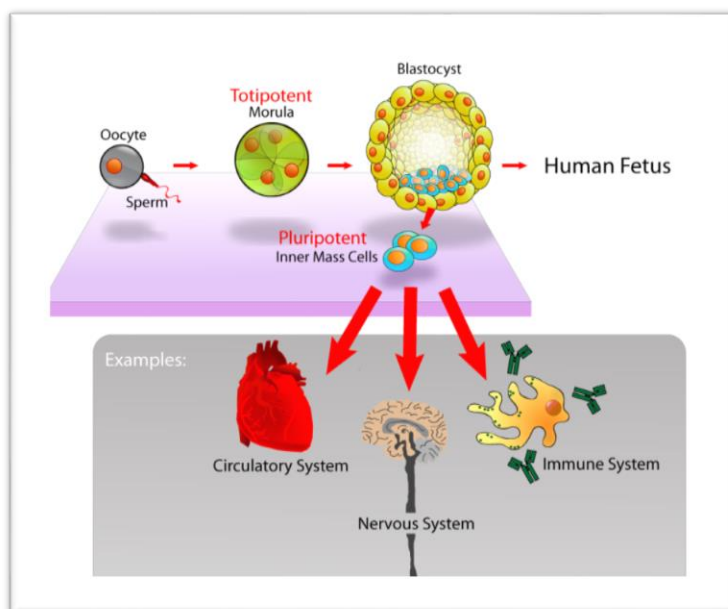
Multipotent stem cells refer to the group of stem cells which can give rise to a limited number of specialised cells within the body but only those of a closely related family of cells. These other types of cells which the multipotent stem cell produces are also limited in number.

Multipotent stem cells can be found in our bone marrow, for example, where different types of blood cells are produced but where the potency and amount begin to fade with time.

2.2 Where are Stem Cells found?

As described above there are different types of stem cells, which originate in different locations within the body of a multi-cellular being. Stem cells are most commonly defined by the stage of development of the organism from which they are derived. Due to this scientists generally prefer to work with embryonic, foetal and adult stem cells, depending on the source of these cells (3).

Figure 1: The Formation of Embryonic Stem Cells (5)



1. Embryonic Stem Cells (ESCs)

Stem cells which originate from an embryo are known as Embryonic Stem Cells. These cells are formed and extracted within the first 4 to 5 days after fertilization has occurred. Depending on how soon the stem cells are taken, the resulting potency and ability to differentiate of the stem cells changes from totipotency to pluripotency. This will be explored in more detail in the next chapter.

Embryonic stem cells have been the centre of the majority of scientific and medical research since the 1980s (2), when the first embryonic stem cell line was created from a hamster. ESCs have since been hailed as the golden standard for all stem cells, as these particular stem cells are, to date, the most potent and possess the ability to differentiate indefinitely into all types of cells.

Essential to the debate concerning stem cells, indeed of paramount importance to many who oppose using embryonic stem cells, is that through the procedure of acquiring these pluripotent stem cells the embryo is "**disaggregated and destroyed**" (6).

2. Foetal Stem Cells

These kinds of stem cells are derived from the tissue of aborted foetuses within the time frame of five to nine weeks post-fertilization (3). These kinds of stem cells are described as being multipotent. However it has been found in some cases that they are able to differentiate into a wider variety of cells than their adult counterparts (3).

There have also been some instances where foetal stem cells act in a pluripotent manner, such as when they are derived from foetal reproductive tissue. According to the Irish Council for Bioethics' Stem Cell Report, "scientists have discovered stem cells in amniotic fluid, which surrounds the unborn foetus" (3) and which are pluripotent in nature.

3. Adult Stem Cells

It is presumed by many that these kinds of stem cells relate only to those over a certain age - this is not the case. Adult stem cells refer to stem cells obtained from babies, children, adults, and "even in umbilical cord blood" (3). These stem cells can be obtained from numerous locations around the human body; bone marrow, skin, the brain, blood, eyes, liver, and hair. Due to the fact that these stem cells have already differentiated to some extent during the organism's life-span, their ability to become a multitude of cells is limited. As such, adult stem cells are described as being multipotent in their ability to differentiate.

4. Induced Pluripotent Stem Cells

An important point to note here would be that in the last decade research into the differentiating ability of adult stem cells has been extensive due to the pressure placed on researchers to find a more ethical way of obtaining pluripotent stem cells - namely, a method whereby no loss of life or even the potential loss of life could occur.

The first glimpse of the potential of adult stem cells was not recognised until 2006, when Shinya Yamanaka and his team managed to **reprogram** adult stem cells into pluripotent stem cells, which as outlined above equates these new stem cells to embryonic stem cells. This reprogramming was achieved through the addition of four specific transcription factors which altered the biological programming of the adult cell, thereby causing it to act as if it were an embryonic stem cell (7). These newly reprogrammed cells are now known as **Induced Pluripotent Stem Cells** and will be explored in greater detail in the following chapters.

2.3 The Possibilities of Stem Cell Therapies

"There is nearly universal agreement in the scientific community that stem cell research should contribute to the alleviation of human suffering and disease" (8). The possibilities of stem cell research are at times awe-inspiring, with promises of future applications which will cure all kinds of ailments, injuries, diseases, as well as other social constructs such as old age (interview source). While controversy surrounds the method of obtaining embryonic stem cells, it is vital for the continuation of research into this important area of medical science, that the possibilities which stem cells could offer are thoroughly explored and communicated clearly to inform public opinion.

1. Understanding Cells

As highlighted above, stem cells are the originating cells of all humans. It is from these few cells whereby a complete organism comes into being through the process of cell differentiation.

Cell differentiation has eluded the scientific grasp for decades, but with the advent of stem cell lines research has taken on a new edge.

This is because diseases such as cancer or conditions arising from birth defects are thought to occur because of problems in the differentiation process, and so "an understanding of the development that happens in normal cells will help scientists treat the developmental errors that can occur" in cells affected by disease (2).

Researchers are now able to efficiently produce all of the different kinds of body cells which make up the human organism - neurons, skin cells, blood cells, muscle, bone etc. With this abundance of material, those who were once hampered by lack of resources can now attempt to fully explore the functions of these cells, how they differentiate, and their applications.

2. Treatment of Disease

Stem cell research possesses the potential to discover cures and effective targeted treatments for some of the worst degenerative and debilitating diseases, as well as permanent injuries. Researchers are now able to develop stem cell lines with particular mutations in order to experiment with alternative cures. The main diseases which have captured the focus of stem cell research are heart disease, cancer, diabetes, Parkinson's, and Alzheimer's (2). It is hoped that stem cell research will aid the search for clinical cures or treatments for many, if not all, of the life threatening diseases currently known to exist.

3. Patient Specific Therapy

One of the main problems associated with tissue transplants or organ donation whereby the donated organ is rejected by the receiving body. This is called an immune reaction, whereby the patient's body attacks the new cells, which are recognised as foreign. This recognition is due to the antigens on the new cells' surfaces; "Antigens, which are present on the surface of cells, are the signals by which the immune system recognises external cells and proceeds to reject them" (3).

It is believed that embryonic stem cells "have an advantage over stem cells from the adult body because they express less antigen molecules on their cell surface" (3), and thus may escape immune rejection.

The difference with adult stem cells is that these can potentially be taken from the same body which they are then injected into, which would not produce as much of an immune response and rejection. This approach is referred to as 'patient specific therapy' (3).

Bearing this therapy in mind, it is believed by some that "the derivation of embryonic stem cells represents a major advance towards the development of personalized medicine" (4). Theoretically every person on the planet would have a personal bank of stem cells, ready to be utilised for any kind of medical emergency.

4. Renewable Resource of Tissue and Organs

"Today, donated tissues and organs are often used to replace damaged tissue, but the need for transplantable tissues and organs outweighs the available supply" (7). Stem cells hold the potential to offer a renewable source of both tissue and organs. If this were to come to pass, the social consequences could be enormous, ranging from the eradication of the black market in organ procurement commerce to a reduction in patient death rates which are due to lack of organ or tissue donations.

"For those suffering from serious diseases, stem cells offer hope for effective treatment or perhaps even a reversal of the disease," or of age itself (2). However, as exciting as these applications are, they are still in the primary stages of their full realization and a lot more intensive research is required.

3. Introduction to Embryonic Stem Cells

This chapter will be dedicated to thoroughly exploring the diverse opinions which have shaped and informed the embryonic stem cell debate as well as obtaining a better understanding of ESC history. This foundation will establish the ethical and legal issues which will then be explored in further detail within chapters four and five as well as receive critical commentary therein.

3.1 History and Discovery of Embryonic Stem Cells

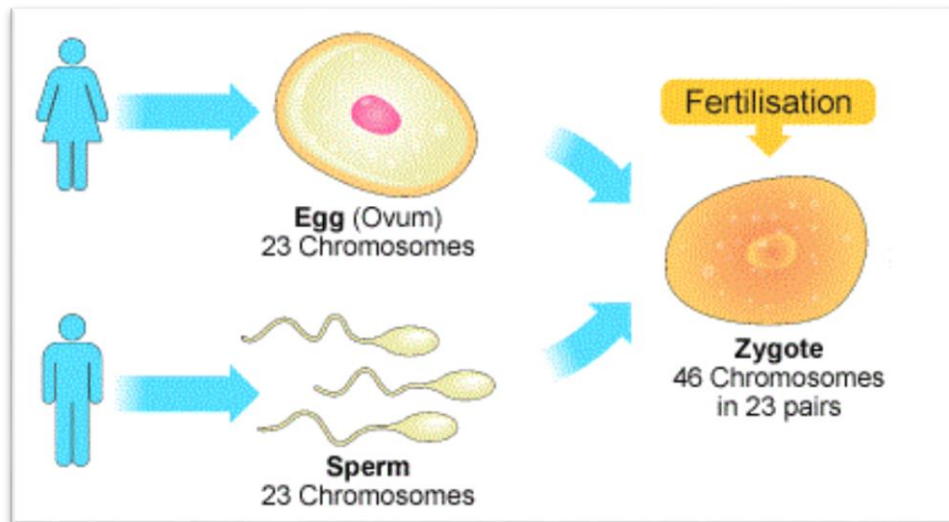
Built upon decades of extensive research, the history and trajectory of embryonic stem cells is tremendous. Stem cell research was first reported in attempts to fertilise mammalian eggs outside the body in 1878 (9). Subsequently the rapid evolution in medical understanding and knowledge contributed to ongoing stem cell research, development and refinement of techniques and processes. A time line - Appendix 1 : U.S. Department of Health and Services, is a useful reference point for the remainder of this paper (9).

Embryonic stem cells are stem cells which originate from an embryo. Intricately linked to ethical and legal issues in relation to this kind of medical research, are the different stages of development, whereby ESCs can be obtained. Although many would assume that such biological detail is superfluous, it will become apparent through later exegesis of the ethical and legal issues that these minute details have been the main, if not deciding, influence on the many differing opinions in relation to the embryonic stem cell debate.

Starting from just before conception, there exists two separate sex cells, an ovum produced by the female human and a sperm which is produced by the male human. Each of these sex cells contains 23 chromosomes. For reference purposes, every single cell in the human body for any human being, apart from these sex cells, contains 46 chromosomes. This is our biological make up.

Once these two sex cells fuse through a process known as fertilization, a zygote is formed which now comprises both sets of 23 chromosomes, thereby 46 chromosomes in total; "the full complement of the human genome" (3). Enough necessary to proceed with embryogenesis. (See figure 2)

Figure 2: The Process of Fertilisation (5)



According to the 2012 Irish Council of Bioethics' Stem Cell Report (3), "Embryogenesis spans from the end of fertilisation (zygote stage) until the end of the eighth week of development, after which the developing human is referred to as a foetus" (3). It is important to note here that the labels which are used to denote the different stages of development of the zygote are not entirely set in stone; It has been argued that terms such as 'pre-embryo', which is usually employed to describe the zygote during the first 14 days of embryogenesis, is an attempt to distance the researchers from the possibility that they are researching on living humans. This use and manipulation of language will be explored further.

There are four main stages of embryogenesis which are essential to the ESC debate; the formation of the morula, the formation of the blastocyst, implantation, and gastrulation.

1. The Formation of the Morula

Starting with the single cell zygote, a process known as Mitosis begins whereby the cell starts to divide itself into two cells, which then divide into four cells, and so forth. These first few cells of the embryo are described as **Totipotent Stem Cells**, stem cells which possess the ability to differentiate into **all the different kinds of cells** within the human body, and so are able to give rise to an entire organism. If the cell group splits at this stage identical twins or triplets can begin to develop (8). Some view this as the defining moment in the life of the embryo, believing that this is the point where the life of the individual truly begins. Merely four days after fertilization occurred, the cells have divided four or five times resulting in the formation of a "solid ball of 16-32 cells called the Morula" (3).

2. The Formation of the Blastocyst

Over the course of the next day, the Morula begins to hollow out and fill with fluid. These additional characteristics transform it into what is known as the Blastocyst. "The embryo will now develop from a specific cluster of blastocyst cells referred to as the inner cell mass, embryonic disc or embryoblast" (3). These cells are **Pluripotent Stem Cells**, and are able to give rise to all the necessary cell types of the developing embryo. It is usually at this stage of development whereby researchers attempt to retrieve the Pluripotent Stem Cells by isolating the blastocyst and extracting its inner cell mass. It is important to understand that through this process of extraction, the embryo cannot continue with embryogenesis; as some would affirm, it is damaged and irrevocably destroyed.

Figure 3: Formation of the Blastocyst (5)



3. Implantation

Should Blastomere extraction **not** take place, embryogenesis continues uninterrupted; While the zygote has been developing from a Morula into a Blastocyst, it has been travelling from the fallopian tubes of the female reproductive system and, after about 5-6 days since fertilisation, it has reached the uterus and begins to attach to the lining of the uterus i.e. implantation takes place. This process "should be complete by day 12 (usually day 8-10)" (3). Once this process is complete, the embryo continues to develop using the maternal blood supply.

4. Gastrulation

Two weeks after fertilization, the cells of the inner cell mass of the blastocyst begin to form into distinct cell types which will form the embryo. It is at this stage that the embryo is now termed a "Gastrula" and the possibility of twinning is no longer possible. Essential to the debate concerning ESC research is that it is at this point (usually day 14) where the **Primitive Streak** forms; "This structure orients the early embryo, defining its head and tail, and can be described as the precursor of the embryo's vertebral column" (3).

Although the latter two stages do not appear to pertain directly to embryonic stem cell research, they are of utmost importance when debating the controversial ethical issue of when true human life begins for a developing embryo/foetus. For some it may be the case that life begins from the moment of conception, whereas for others this decision is not as straightforward as it may seem.

3.2 Alternative Methods of Obtaining Human Embryonic Stem Cells

Embryonic stem cells have been the centre of nearly all stem cell research since the early 1980s due to their pluripotency and ability to differentiate into all the cells of the human body. The moral issue raised by a multitude of philosophers, scientists and researchers alike ((8),(4),(3), (10), (11), (12)) of the need to destroy an embryo to retrieve embryonic stem cells has led to significant pressure to find morally acceptable alternative sources for such stem cells. New alternative methods of creating or obtaining embryonic-like stem cells are currently being explored.

IVF - In Vitro Surplus / Supernumery IVF Embryos

Researchers can obtain surplus embryos from IVF treatments where couples or individuals undergoing this treatment choose to donate them to stem cell research. In vitro fertilization can be described as a process whereby a couple (or an individual) for some reason or another cannot become pregnant or cannot bring a foetus to term through natural methods, and so need external help to do so. The female goes through hormone treatment which stimulates her ovaries and causes them to produce an abundance of eggs which are extracted and, in a laboratory culture dish, are combined with the sperm specimen which the respective male participant has provided. The joint ovum and sperm are now known as zygotes because fertilization has occurred. Usually two zygotes are then placed within the female's uterus with the hope that at least one will implant i.e. attach to the uterus. The remaining zygotes are usually cryo-preserved (frozen) for the couple, should they wish to conceive again in the future.

The reason that this particular method of conception is well known as a source of embryonic stem cells is because of the multitude of spare zygotes which have been stored by these couples. These are known as Supernumery IVF Embryos (3) and provide stem cell researchers with an alternative source of embryos needed to extract Embryonic Stem Cells.

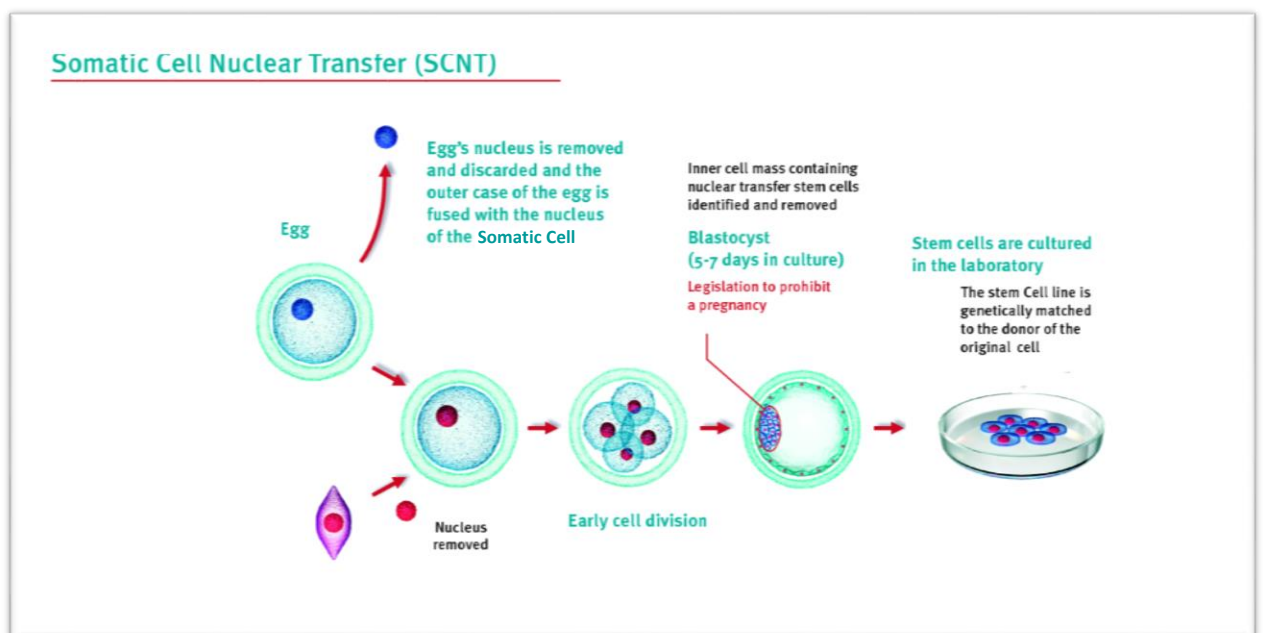
Controversy still surrounds this procedure, as many argue that even though the embryo exists outside of the uterus it is still alive and thus using these embryos is just as immoral as using embryos conceived through natural methods.

This argument is explored through the Potentiality Argument section, whereby the consequentialist understanding of the embryo's life is determinant of the degree of moral status which it acquires; thus in the case of embryos created specifically for research purposes (and which will never be born or develop past a certain point) no moral status is ascribed (3, 13).

SCNT - Somatic Cell Nuclear Transfer

Also known as "therapeutic cloning" (8), SCNT "was first used 40 years ago in research on tadpoles and frogs" (3) whereby scientists were attempting to understand gene expression and "whether genes necessary for development could be switched back on in differentiated adult cells in which they had long ceased to function" (3). Their conclusion was affirmative; that SCNT "effectively reset the gene expression of a differentiated somatic cell to a state consistent with embryonic development" (3).

Figure 4: Somatic Cell Nuclear Transfer (5)



Succinctly, SCNT is a procedure whereby a "technician removes the nucleus of a somatic cell and inserts it into an enucleated oocyte termed a cytoplasm, where the egg cytoplasm reprograms the transferred donor nucleus" (8) into thinking and acting as if it is an embryonic cell.

This "new embryonic cell" then undergoes normal cell mitosis (which, as the nucleus now believes it is an embryonic cell, may be called embryogenesis) which culminates in a blastocyst forming, and thus an inner cell mass which can be harnessed for pluripotent stem cells. See Figure 3. A central ethical concern at this stage is the amount of eggs which will be needed for such a method to be used worldwide. This topic is further explored with reference to the commercialisation of human eggs and embryos.

ANT - Altered Nuclear Transfer

Altered Nuclear Transfer was proposed by William Hurlbut in 2005. It is an alternative approach to therapeutic cloning, with which Hurlbut attempted to bypass the ethical controversies of producing cloned human embryos to obtain patient specific embryonic stem cells (3). The technique is exactly the same as SCNT, with the only difference being that a gene which is necessary for embryo implantation is genetically altered in the donor nucleus *before it is transferred into the egg cytoplasm* (3). This genetic modification is achieved using a technique called RNA interference whereby researchers disrupt a gene called Cdx2, which enables an embryo to grow a placenta (3).

Once the remainder of the SCNT process is completed and the embryo begins to form, due to the genetic modification it will be unable to develop a placenta and thus will be unable to implant. Theoretically it can be argued that as the embryo cannot, indeed will never be able to, implant and naturally develop into a human then no loss of potential life occurs when the embryonic stem cells are harvested. As Hurlbut asserts, a human embryo created by ANT would be a biological entity "that lacks the attributes and capacity of the human embryo" (3) and thus cannot be conceived of as being a potential human. In the eyes of the author it appears that Hurlbut does not take into account that this kind of deliberate debilitation of what could be a viable embryo is just as morally wrong as using viable embryos to harness stem cells in the first place. The reasoning for this is explored further on.

The main scientific disadvantage for this alternative source of embryonic stem cells is that while it has been achieved successfully through research studies on mice (3), scientists have yet to fully evaluate the impact this genetic modification has on potential stem cell development. As well as this, researchers are not fully convinced that Cdx2 is the only gene which effects embryo/placenta development (3).

Single Cell Blastomere Extraction

Modelled on PGD (Pre-implantation Genetic Diagnosis) methods, single cell Blastomere extraction refers to the process of taking a single cell from an eight cell IVF embryo and using it to establish a stem cell line. This process is similar to PGD in the way that it is at exactly the same stage of development whereby a single cell is extracted from the eight celled embryo. The only difference is that in the case of PGD this cell is tested for genetic abnormalities which may inform the parents about the embryo's genetic make-up. The leading advantage of this method is that the remaining seven cell embryo could still potentially be used to treat infertility (3). Tested on mice, whereby the same procedure occurred, the remaining seven celled embryos were transferred to the surrogate mother's womb and were carried to term, with no discernible defects (3). Although this new method seems promising, given the relatively young age of PGD long term studies of its implications have yet to be conducted and so single cell blastomere extraction seems less likely to be the chosen alternative until such research is concluded (3).

A major ethical issue for this alternative method of obtaining human embryonic stem cells is that the cell which is extracted from the eight cell stage might still possess the potential of a Totipotent cell; thereby possessing the ability to become a viable human embryo itself (3). Although this has only been established in rabbits and sheep, the possibility that a human could potentially form from this single cell has been levelled with the same charge which the method was attempting to bypass; namely, that destroying an organism (the Totipotent cell) which could potentially become a human (or is a human depending on the view given) is highly immoral (3).

Somatic Cell De-Differentiation

One of the main methods for obtaining human embryonic stem cells is through cell de-differentiation. Where cell differentiation refers to the process by which cells become specialized to a particular role within the human body, cell de-differentiation refers to the complete opposite; namely, that the cells revert to a less specialized role. As this method of obtaining stem cells does not require the destruction of a human embryo, a strong argument can be made proposing this line of research as opposed to that of human embryonic stem cell research, as it appears to circumvent many of the ethical and legal challenges posed by the latter.

Whether this alternative approach actually *does* help resolve these issues is the question at the forefront of this thesis. Prior to grappling with the sensitive ethical and legal issues which human embryonic stem cell research conjures, an in-depth understanding of the leading somatic cell de-differentiation technique needs to be explored; namely, Induced Pluripotent Stem Cell research.

4. Introduction to Induced Pluripotent Stem Cells

While human embryonic stem cell research continued to face ethical and legal barriers, researchers from the medical profession sought a more ethically acceptable means of obtaining stem cells, in particular stem cells which could replicate the efficiency and potency of human embryonic stem cells. Prior to the medical breakthrough by which iPS cells were produced, the preferred method of obtaining human embryo-like stem cells without major ethical or legal implications was SCNT. That said, SCNT poses its own economical and ethical problems as it requires a great supply of non-fertilized human eggs, which will receive further analysis in chapter four. Thus, the search for a better means of procuring human embryonic stem cells without the dubious ethical and legal complications continued. Based on years of human embryonic stem cell research as well as extensive analysis into the differential process of human body cells, a breakthrough occurred within the area of somatic cell de-differentiation.

4.1 Discovery of Induced Pluripotent Stem Cells

In 1962, John B. Gurdon demonstrated that the nucleus from a differentiated frog intestinal epithelial cell can generate a fully functional tadpole via transplantation to an enucleated egg. Gurdon used somatic cell nuclear transfer (SCNT) as a method to understand reprogramming and how cells change in specialization. He concluded that differentiated somatic cell nuclei had the potential to revert to pluripotency. This paradigm shift in the understanding of the differential capacity of cells stimulated the extensive research into de-differentiating human body cells.

Just over half a century later, in 2007, three research groups, based in Japan and the United States, confirmed a new method of obtaining stem cells which possessed similar efficacy and potency as embryonic stem cells (3, 14). Of the three researcher groups, Shinya Yamanaka and his team, in Kyoto University Japan, were the first to generate these new cells using mouse fibroblasts in 2006.

The following year, in November 2007, Yamanaka and his team were able to apply the experimental new method to human somatic cells which resulted in the successful production of human embryonic-like stem cells (3).

Meanwhile, in the United States, at around the same time, James Thomson at University of Wisconsin-Madison achieved the same result helping to validate the results achieved by the Japanese team (15).

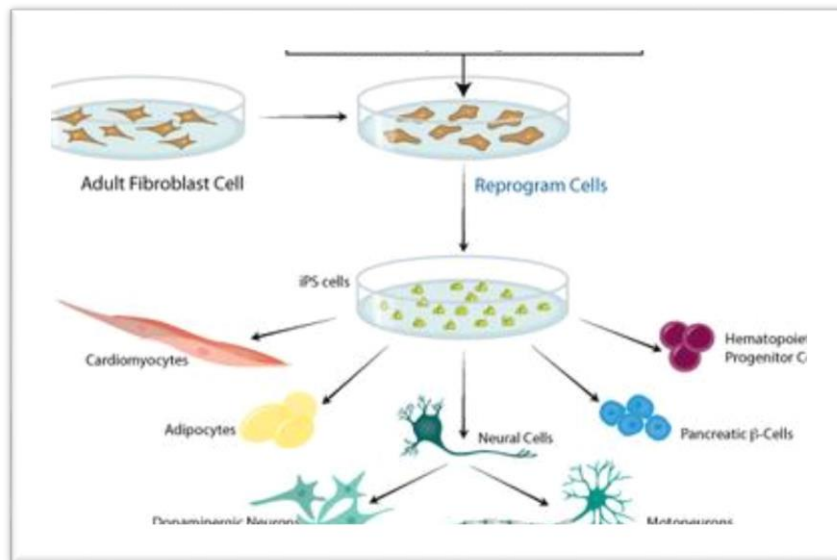
4.2 Methods of Creating Induced Pluripotent Stem Cells

The methods followed by each of the Yamanaka and Thomson research groups are quite similar, in that the general approach specified that three or four specific human genes, also known as transcription factors, found previously to be important for development could be expressed within the somatic cells and in turn coax them into an embryonic cell-like state (3). Transcription factors are proteins involved in the process of converting, or transcribing, DNA into RNA within a cell. These factors regulate the gene expression within cells by reading and interpreting the genetic 'blueprint' within the cell's DNA, thereby directly influencing the role and differentiation capacity of the cell.

To fully appreciate the exhaustive measures that were applied to discovering these factors, a brief exploration of the gruelling process of elimination employed by Yamanaka and his team must be acknowledged. Starting with a list of over 100 possible transcription factors, unsure of whether these factors acted alone or need to be employed in conjunction with another specific factor or multiple factors, Yamanaka began the process of whittling down the list of over one million combinations which could lead to cell de-differentiation (7). Through the use of a computer program he was able to identify 24 of the most likely factors able to stimulate de-differentiation. Through years of research, Yamanaka and his team were able to identify four transcription factors which normally only act together within an embryonic stem cell; Oct3/4, Sox2, Klf4, and c-Myc. These four factors were then placed into a skin cell. In a process which was not fully understood at the time and is still being explored, the chromosomes within the skin cell began to unravel.

By doing so, the factors which were introduced to the cell could attach to the genes of the cell and overwhelmed the competing message from the skin genes, thereby tricking the cell into believing it was in an embryonic environment. As these pre-programmed cells replicated, they became more like embryonic stem cells, until they were indistinguishable from them.

Figure 5: Production of Induced Pluripotent Stem Cells (5)



Although both Yamanaka and Thomson applied similar methodology in achieving their aims, both teams utilized different proteins/genes and viral systems to attempt to de-differentiate the human fibroblasts. These systems were needed to insert the transcription factors into the cell. Where on the one hand Yamanaka employed four pivotal human genes, namely Oct3/4, Sox2, Klf4, and c-Myc, through a *retroviral* system. Thomson and his team, on the other hand, chose to apply OCT4, SOX2, NANOG, and LIN28, using a *lentiviral* system. While it can be argued that both combinations of factors achieve a similar result, the process has yet to be perfected and the use of each individual factor may produce unwanted side effects in the resulting stem cell (16).

4.3 Possibilities of Induced Pluripotent Stem Cells

Aside from the possibility that induced pluripotent stem cells could limit the need for embryonic stem cells, the consequences of producing induced pluripotent stem cells are far reaching and positive. Due to the fact that they are able to give rise to all three germ layers of the developing embryo, i.e. being pluripotent in nature, induced pluripotent stem cells appear to alleviate many medical problems associated specifically with supply shortages in many areas. Such as, organ donation, blood donations, and even reproductive cell donations (4). Coupled with their potential to proliferate infinitely, iPS cells seem almost miraculous in their possible applications.

Through the discovery of Park *et al* that human cells from various sources are able to be reprogrammed (3, 8), cellular de-differentiation holds much potential and promise for developing patient specific stem cells (8). Such specifically designed stem cells may be utilized to treat patients individually, using their own somatic skin cells as the starting point of producing their own personal stem cells. By doing this, it has been proposed that immune-rejection of stem cells could be very much reduced, as the stem cells will possess similar, if not identical, genetic information as the host organism as well as similar surface antigens which are the primary trigger for immune rejection (11). This medical technology could potentially revolutionize the healthcare industry worldwide, not only through the use of a patient's specific stem cells but also through the ease of obtaining these stem cells through the patient's own somatic cells. Following treatment the stem cell line may be stored in a stem cell bank for easy access in the future.

Not only that, but the production of disease specific cells through the production of stem cells will greatly enhance the speed and precision of researchers attempting to identify and treat some of the world's most degenerating diseases, for example Alzheimer's and Parkinson's Disease (4). A particular setback in relation to this field of research is the inability of researchers to apply new found discoveries to human patients with the disease. With the introduction of disease specific stem cells, researchers will have an abundance of infected human cells with which new cures or treatments may be tested upon. This aspect of induced pluripotent stem cells is a driving force behind the research taking place.

Not only will this application eliminate the need to test certain cures or treatments on purposefully infected animals, but it may speed up the process of releasing said cures to the human public, as it may reduce the amount of time needed for human clinical trials.

4.4 Problems Associated with the Creation of iPS Cells

While the newly reprogrammed cells appear similar to embryonic stem cells in terms of their morphology, efficiency, and potency potential (3), this new method poses its own problems.

Using ESCs as the “Golden Standard” of what pluripotent cells should be capable of, researchers and critics of induced pluripotent stem cell research have been able to highlight areas of significant concern within the methods and consequences of creating induced pluripotent stem cells.

Although the main contributory transcription factors needed to create induced pluripotent stem cells have been identified, little is known concerning any future repercussions of their employment. Of primary import is that expression of these factors within the fibroblast could possibly lead to tumour formation (3). As well as this, the efficiency of converting somatic cells to iPS cells is still relatively low, meaning that while the possibilities seem endless, their achievement might be further away than anticipated (17).

Until safer and more stabilized means of inducing pluripotency is discovered, human clinical trials which are necessary prior to approval for real-world application will not be allowed to take place and thus all the possible advantages of induced pluripotent research, including the possibility of an ethical alternative method of creating human embryonic stem cells, will remain unachievable.

As important as these biological and scientific issues are, the question of this thesis remains: do induced pluripotent stem cells resolve the ethical and legal dilemmas posed by embryonic stem cell research? The following chapters seek to analyze and compare both embryonic and induced pluripotent stem cells in an effort to offer an answer to this question. Specific attention will be paid to the ethical and legal foundational issues of embryonic stem cells, which iPS cell research is seeking to overcome through its employment.

5. Ethical Issues of Human Embryonic Stem Cells

The central line of inquiry of this thesis is whether induced pluripotent stem cells are truly able to alleviate the ethical and legal dilemmas posed by current human embryonic stem cell research methods. In order to do this accurately, the central ethical and legal issues of human embryonic stem cells which induced pluripotent stem cells claim to resolve require analysis. This chapter will focus on the ethical issues of human embryonic stem cells.

5.1 Where Does Life Begin?

Using human embryonic stem cells to further medical knowledge is a leading issue within this debate. This is due to the fact that through the method of obtaining human embryonic stem cells from the blastocyst, the embryo is destroyed. Whilst proponents who are interested in furthering scientific knowledge accept this with little (it seems) moral question, opponents find it difficult to grapple with. To them, it is evil and immoral, and they fervently oppose it. Due to this, the science of stem cells has been drawn into the highly divisive debates concerning the interpretation of life. These debates have existed within the legal and political spheres for the last three decades (18).

This part of the human embryonic stem cell controversy can be succinctly described as a debate concerning the point at which a zygote, embryo or foetus (depending on the opinion given), gains moral status as a human being - thus, becoming or being endowed with all the social endowments and protections this affords, for example, the right to life, dignity, personhood *etc.* Through examination of the relevant literature and research, it becomes apparent that there are three main categories which encompass the general popular opinions in relation to this issue: (18, 19)

Table 1: Categories of When Personhood is Ascribed

<p>Full Status From Conception</p>	<ul style="list-style-type: none">•Advocates from this group believe that from the moment of conception / fertilization the embryo "is a new human being or individual with all the rights and legal and moral status of fully born persons".•These groups view destruction of embryos, including abortion, as murder, "as a sacrifice of the weakest amongs us for the interests of others" .•They continue to uphold their sanctity of life arguement, even where supernumery embryos, which are to be discarded anyway, could be used for research purposes.
<p>Gradualist</p>	<ul style="list-style-type: none">•The gradualist approach is summarised as one which "is somewhere between [the other two] and holds that the embryo is human tissue with the potential for human life, and thus deserves respect".•This group has multiple understandings of the point at which the embryo becomes endowed with personhood. This is due to cultural, religious and social reasons which are highlighted below.•The gradualist group has also been described as those who "believe that [embryos] gradually gain moral status as they develop" (rte.ie/science), and can also believe the embryo to be deserving of special limited rights.
<p>No Status</p>	<ul style="list-style-type: none">•Proponents from this category view the "embryo as too rudimentaty in development to have interests or rights, and thus [believe] that they should not be protected at the cost of legitimate and important scientific research".•For this group, no real sacrafice is taking place as the embryo is not alive and so does not theoretically 'lose out' on life or dignity.•Those who view human embryonic stem cell research with this perception of early embryos, do not find it difficult, indeed can believe it to be a moral obligation to use embryos which would otherwise be aborted or discarded for research purposes.

Certain factors and influences from the social and cultural aspects of individuals' lives have helped shape the above understandings of when or whether an embryo deserves certain rights and protections. A deeper examination of these factors will help illuminate the reasons as to why this aspect of the stem cell debate has such considerable implications.

Religious Influences

Religion plays a major role in influencing the moral codes employed by individuals; for centuries it has been the moral compass which has denounced immoral acts and upheld, even encouraged, basic rights at times when no other institution did. For example, the Golden Rule , *do unto others as you would have them do unto you*, has formed a solid moral basis for many, if not all, religions in some way or form. As a social construct, it has given voice to the innate moral capacity which humanity possesses with regards to maintaining and promoting life.

Generally those of the first category, Full Status from Conception, are active members of their religious community and faith. It is usually this group who view all human bodies, no matter what the circumstances, be it age, social status, race, or biological development, to be of equal value and fully endowed with human rights.

This perception of personhood and moral status closely mirrors the way which conservative Catholicism views the debate on when life begins (3). For the Roman Catholic body, each individual is to be seen as an image of God himself, one who must always be treated as an end in himself or herself, not merely as a means to other ends (20). A paper written and published by the Pontifical Academy for Life (21), found on the Vatican's website, explores the Catholic perspective of stem cell research, and succinctly summarises (with reference to both the *Evangelium Vitae* and the *Donum Vitae*) that:

"The Church has always taught and continues to teach that the result of human procreation, **from the first moment of its existence**, must be guaranteed that unconditional respect which is morally due to the human being in his or her totality and unity in body and spirit: The human being is to be respected and treated as a person from the moment of conception; and therefore from that same moment his rights as a person must be recognized, among which in the first place is the inviolable right of every innocent human being to life" (21).

Dating to the 17th Century, when Pope Pius IX dropped the distinction between the *foetus inanimatus* and the *foetus animatus*, the Catholic church has maintained its faith in the sanctity of life; namely that from the moment of conception, an embryo should be accorded full moral status (3). There exist other bodies which support this view of the embryo, such as Eastern Orthodox Christians (3).

Another main religious body, namely Islam, holds quite contrary views to that of Catholicism. Perhaps not quite in the Gradualist group, the Islamic faith stands somewhere along the border between full rights for the unborn and advocating the necessity of human embryonic stem cell research, through which an early embryo is destroyed. It has been advocated by Islamic scholars that it is their religious duty to pursue and consider medical research which is directed towards discovering new treatments which could alleviate disease or improve health (19). For some Muslims the possibility of using embryos in a therapeutic manner to save human life causes the act of human embryonic stem cell research to be seen as a collective religious obligation (*fard kifaya*) (19).

Thus, stem cell research has been received with a more open mindset than other, more traditional and morally entrenched religions. Muslim scholars rely on independent judgement (*ijtihad*) of verses found in the Qur'an or the *Hadith* (a book of the sayings and actions of the Prophet Muhammad) when faced with a modern day development which has no precedent in these primary sources. Therefore where stem cells appear to jeopardise the life of an unborn child, the query is one of where life begins (although this formation of the ethical issue is not exclusive to Islam).

Islamic scholars describe the development of the embryo in two phases; namely, biological and human. Through a process of **ensoulment**, which is believed to be God breathing the soul of the being into the foetus, the two phases are differentiated. Hence for Muslims, biological life starts at fertilization, but human life begins after ensoulment. The main question here is: when exactly does ensoulment take place? According to one verse in the *Hadith*, some scholars have identified the timing of ensoulment to take place when the embryo is 40 days old.

Depending on the interpretation, this could be extended to 120 days as the verse could be understood as describing three 40 day periods which the embryo must go through prior to ensoulment.

Interestingly enough, if one were to assume that ensoulment takes place on the 120th day, this corresponds more or less with the majority of worldwide legislation concerning the cut-off point of carrying out an abortion; generally the cut off point for legal abortions is around the 14 - 18 week mark, which equates to the 98 - 126 day mark.

A more critical question related to the incorporation of religious influences into this debate would be: is it absolutely necessary to do this? Through the ages, the religious definitions of what it means to be a person have changed significantly based on the cultural perceptions and intellect of the times; Aristotle for example employed a dualistic view of the person - defining the person as a "rational animal", acknowledging that a human person is at the same time a material being as well as a spiritual one (22). This interpretation however is not the only one which has permeated religious history. Nearly each religion has its own perception of the relationship between a person and his/her soul, whether they entwine as one from the moment of conception or whether ensoulment, as is the case in Islam, occurs later on during embryogenesis. Due to this it is the view of the author that while religious interpretations may influence opinions concerning embryonic stem cell research, it must not be the authoritative guide on the permissibility of the act.

Definitions and Interpretations

Definitions and interpretations, coloured by cultural and personal experience, can often cloud our understanding of this complex topic. Due to the plethora of conflicting opinions attached to specific phrases or words, definitions within the stem cell debate have appeared elusive to say the least, and limited in their scope at the most.

A central term which is often employed in this debate and which appears to lack a solid definition is that of 'person' or 'personhood'. Intimately linked with this term, are the attributes which define exactly what it refers to.

Philosophers John Locke and Thomas Aquinas believe that certain metaphysical attributes exist which may help to define whether an embryo is a person and thus deserving of protection and fundamental human rights (23, 24). They explore this throughout their works and theorise that only a human *person* may possess the fundamental capacities necessary to exhibit the essence of what it means to be a living human, demanding respect and possessing an innate dignity .In embryonic stem cell research, this idea of personhood is employed to both propose and oppose the destruction of the embryo for research purposes.

At first this term seems to carry only the simplest definition, but a further exploration of the complex nature to which it refers will convey the degree to which it convolutes the stem cell debate. A central problem with the term "person" or "personhood", one which is shared with all other terms used within this debate, is that it appears to lack a clear and definitive explanation of what it refers to. Hence multiple interpretations of the term have been advocated in conjunction with the above categories of status i.e. depending on the opinionated group's perception of the embryo's moral status.

As explored above, opponents of human embryonic stem cell research base their opposition on the fact that an embryo is a human person from the moment conception takes place; from this moment on the zygote or embryo possesses a moral status correlated with an innate human dignity and thus deserving of all the human rights which those of us who are already born enjoy. Those against human embryonic stem cell research affirm that it is *because* the embryo is a human person (thus deserving the same degree of human rights and protections) that no research should be conducted on it regardless of the outcome (7). Immanuel Kant is the oft-quoted philosopher with regards to this side of the argument. As part of his *Groundwork of the Metaphysics of Morals* (25), Kant proposes the Categorical Imperative, a moral law that is unconditional or absolute for all agents. While the scope of this thesis cannot possibly hope to explore the full theory behind this moral imperative, the third condition of the CI succinctly advocates the rationale of those opposed to human embryonic stem cells; "Act so that you treat humanity, whether in your own person or in that of another, always as an end and never as a means only" (25).

Peter Singer, an Australian utilitarian bioethicist, argues that this point may not be as persuasive as it is believed to be. He makes a strong case that the *kind of species* to which the embryo belongs, does not directly influence the morality of using the embryo for research purposes. Rather, he affirms that it is the *type* of being which has influence of this kind (26). Dismissing the assumption that just because one will be born human he/she deserves full moral recognition and status. Singer, (as well as other philosophers such as John Locke) have presented this argument in the light that in order for a being to be classified as a person, certain empirical and cognitive faculties need be possessed by these beings. Note the exclusion of the word human, as there are other possible beings which could also possess these faculties. These faculties, succinctly described by David de Grazia (27), include complex forms of consciousness such as autonomy, rationality, self-awareness of one's place in time, linguistic competence, morality and sociability (27). Separately, Singer proposes characteristics which de Grazia either intentionally excludes, or has not considered; namely, consciousness and the capacity to experience suffering. For these philosophers the definition of personhood or the debate on whether an embryo is a person, depends on the embryo's ability and capacity to possess these cognitive and empirical characteristics of a person, whereas for Kant simply being human is enough to warrant the expectation of being treated with respect.

This kind of bi-polar interpretation is not limited to the area of stem cell research; it occurs once more, for example, in the case of a coma patient; are we to define this patient as a person and respect his/her dignity and moral status as such, or are we authorised to decide on behalf of the patient concerning, for example, life-altering decisions? Generally in such cases those who are believed to be able to advocate for the best interests of the patient are assigned as a proxy decision maker. However in the case of stem cell research, sometimes this is not possible, especially if the embryos are created through SCNT or are donated to science for research purposes. In these cases it appears as if it does not matter that the patient's (embryo's) rights are protected.

It seems to the author that this link has been overlooked to some extent within the stem cell debate and recommends that further exploration is employed to highlight any possible connections which may help inform the rights and/or understanding of the personhood of an embryo.

Other terms exist which cause added confusion within the stem cell debate are those which are used to describe the different stages of embryonic development. While most people can agree that an embryo refers to an unborn human when it comes down to the bare details of zygote to blastocyst, blastocyst to foetus, foetus to embryo, embryo to baby *etc.* the boundary lines are harder to agree upon. Use of these terms, without proper definition can possibly lead to confusion within the discourse, exacerbating certain uninformed perceptions rather than defining clear and concise instruction.

Disagreement on the definition of a person and when human life begins has fuelled the ethical controversy allowing research to be conducted on embryos under the age of two weeks. This refers to the employment of the term 'pre-embryo'. According to Richard M. Doerflinger, textbooks of the late 1980s and some British Laws employed this term in order to differentiate between an early embryo of up to 14 days, and one of later development (20). This definition enabled the foundation for non-therapeutic research on embryos which were younger than two weeks but has since been openly dismissed and discarded (20). Recently this term has been rejected by the Human Embryo Research Panel who are advocates of research performed on embryos under two weeks of age, as well as the National Bioethics Advisory Commission who defined an embryo as "the developing organism from the time of fertilization" (NBAC 1997) (20). The author suggests that this might have been employed as a moral deterrent to pursuing embryonic stem cell research, as the term was arguably employed to distance researchers from what they were doing i.e. destroying an embryo. Indeed, one research paper which focused on the use of this term stated that the phrase 'pre-embryo' was a semantic manipulation aimed at depriving the early embryo of its fundamental biological characteristic of living human being (28). Perhaps this was the reason why the term was, according to Doerflinger, later discontinued and the time it denoted (from fertilization to 14 days old) incorporated into the meaning of early embryo (20).

From the perspective of a gradualist interpretation, it appears to be quite difficult to pinpoint an exact time at which an embryo or foetus gains recognition as a developed being deserving of human rights. Due to the direct proportionality assumed between the development of the embryo and the moral status which it possesses, there exist multiple stages of embryonic development whereby moral status may be endowed:

1. One such stage would be at the formation of the Primitive Streak, at approximately day 14 whereby the embryo is oriented thus beginning the process of Gastrulation. Alongside this with the formation of the Primitive Streak, the possibility of twinning is no longer possible - at this point it is believed that the embryo is now described as a **unique individual**, rather than an entity which may become more than one being (3). This view begs the question: at which stage of development do twins or triplets become unique individuals? Is there a different point of ensoulment which possible takes place or are such individuals only able to become separate entities once they are outside of development and have experienced the world?
2. Another possible stage which gradualists may agree upon would be the point at which the embryo implants into the mother's uterus (3). Occurring just before the formation of the Primitive Streak, implantation is a defining moment in the development of the embryo. It is through this biological connection that the embryo can receive nutrients needed to progress with the pregnancy. However this also causes one to pause; would a human necessarily need to be able to receive nourishment and convey signs of sustaining life to be defined as a person? If this were the case, then defining the ethical and legal rights relating to personhood of a coma patient, who also receives nutrition from an external source, would need to be re-evaluated.
3. Two other main stages which may cause some to consider granting the embryo a degree of moral status would be the formation of the neural tube (around 18 days), i.e. the structure from which the brain and spinal cord form, and the onset of the foetal heartbeat (around 2 days) (3).

In a way, this could be correlated to the multiple definitions of death which exist currently; brain stem death, biological death, and legal death. The author argues that if it is possible for us to define a precise point of death, whereby a human loses personhood status (arguably), then by extension this may help with the identification of the point whereby a person acquires personhood status.

With such a vast account conflicting definitions, it is difficult to pinpoint which one succinctly defines the point at which an embryo, which has been established as a living cell, can be afforded moral status or what kind of rights it is entitled to and when.

Potentiality Argument of the Embryo

The Potentiality Argument is employed mainly by opponents to human embryonic stem cell research. The essence of the argument is that even though an embryo, under 14 days of age, is unable to communicate or employ the necessary characteristics some people would state are required for moral status to be conveyed e.g. Aquinas and Locke (as explored above), the embryo has the **potential** to one day develop into a fully functional, rational, linguistic, social being, one fully deserving of moral status and the associated human rights and protections. The author suggests that this argument is a strong statement; why wait to endow moral status on a being which we know has the capability to develop into a human being? Assuming, of course, no outside interferences diminish or restrict this development. As outlined in the Irish Council of Bioethics' Stem Cell Report, even if embryos do not qualify for fully fledged personhood, the argument can be made that their potential to become human beings should affect the considerations given to their moral status (3).

A central problem with this argument is that it can be applied to other situations and contexts which highlight its weaknesses. For example, many of us have the potential to become criminals, yet it would seem unreasonable to treat us as if we were unless we actually fulfil this potential (3). It has been argued that this is a serious logical flaw to the Potentiality Argument; that moral status is to be grounded on the actual properties of a being, not the potential which the being possesses (3).

If the latter were the case, it would be nearly impossible to afford any human being moral status or rights, based on the fact that we possess multitudes of potential to act or develop in any way we see fit.

An aspect of the potentiality argument is one which takes into account the method through which an embryo is brought to term, or rather, not. The essence of this criticism is that embryos which develop in the womb (*in utero*) possess more potential to develop into humans than do those developed in a laboratory culture dish (*in vitro*). The main discerning feature between the two is that in the latter case purposeful external interventions are needed for the embryo to reach its full potential. Many proponents of human embryonic stem cell research use this as a means to justify using embryos cultured *in vitro* for stem cell research, as their potential is to perish (8). Due to this, the author questions if this means that embryos created *in vitro* are without any kind of moral protections at all phases of development (as limited as it may be)? Is it possible to establish which embryos would have implanted or not, had they been given the chance? Once more it seems as if potential researchers may advocate this 'distinguishing feature' between *in vitro* and *in utero* as an effort to pacify their own moral misgivings for the acts they are performing.

Due to the moral outcry, influenced by religious, political, and interpretive factors, which human embryonic stem cell research generated, scientists and medical researchers endeavoured to find a suitable alternative source of these stem cells.

5.3 Social Issues of Alternative Sources of Human Embryonic Stem Cells

While the search for alternative sources of human embryonic stem cells is both noble and ethical in its aim, when one takes time to assess the morality surrounding such practises, startling ethical controversies arise. It is these controversies which led to more pressure being placed upon the medical field to find a better, more ethical method of obtaining human embryonic stem cells for research purposes.

IVF - In Vitro Surplus / Supernumerary IVF Embryos

As highlighted above an alternative source of human embryonic stem cells lies within supernumerary IVF embryos, or rather surplus embryos which are not implanted into the mother's uterus and which are not going to be stored for future use. Proponents of using these embryos for stem cell research employ both a consequentialist as well as a deontological view of why using these embryos is morally acceptable; their central argument is that these embryos are going to be discarded *anyway* i.e. regardless of whether or not researchers intervene, these embryos are going to be destroyed. Thus, consequentially the embryos meet the same fate, however in the scenario where a researcher is the cause of 'death' the embryo has in some way contributed towards scientific knowledge. This leads to the deontological argument, which is closely linked to the utilitarian thought (i.e. the greatest and best outcome for the most amount of people), whereby scientists and researchers feel as if it is their *duty* to research on these embryos *in order that* the embryos lives are not wasted and/or discarded like something which can be easily replaced, and whereby the larger part of society may benefit. This is proposed by Gene Outka who bases it on the "nothing is lost" principle; This principle was developed by Paul Ramsey who summarised that it may be justified to kill an innocent person if this person was going to die anyway and if this death will save other lives (3).

By employing both a consequentialist and deontological defence for the use of IVF embryos, the author believes that a strong case has been made to quell the moral fears of opponents to this research. Although recourse to the 'nothing is lost' principle is arguable, as indeed *something is lost*, namely, an embryo.

Opponents to this alternative method have a strong deontological viewpoint which conflicts with that of the researchers' vindications. For proponents of the embryo's innate right to life and all its associated protections, it is the *action of purposeful destruction* of the embryo which causes death that creates the ethical unease; i.e. it is the intent to destroy which causes the ethical objection.

That is not to say that the same groups advocate for the discarding of such embryos if they serve no purpose; rather, such groups have been known to propose that all embryos which are produced for assisted human reproductive purposes should be utilised (3). In such a case, the intent would always be that the embryo has a chance to develop (3).

The philosophical question remains unanswered however; is the action of actively destroying the embryo for research purposes the ethical equivalent of discarding the embryo? The Irish Council found in its Stem Cell report that while the former appears morally more objectionable than the latter, the outcome is the same in both cases. Some have even argued that doing nothing, i.e. discarding viable embryos, is just as bad as committing the immoral act (3), thereby usually expanding on this point to advocate the 'Nothing is Lost' principle. In the current case, the author would be in agreement with the conclusion reached by the Irish Council for Bioethics, but would hold onto reservations concerning the 'nothing is lost' principle.

SCNT - Therapeutic Cloning vs. Reproductive Cloning

Another alternative of obtaining human embryonic stem cells for research purposes would be by SCNT. As described above in chapter three, this process involves the insertion of a somatic cell's nucleus into an enucleated egg cell. By doing this, the new cell begins to act as if it is an embryonic stem cell, somehow resetting the already differentiated nucleus to an undifferentiated state.

While this new embryonic cell shares genetic information of the somatic cell, it is not a genetic clone. This is due to the cellular DNA which can be found in the Mitochondria of human cells (8). That said, the new cell could potentially possess enough similar genes to the supplying patient to ensure a limited possibility of immune-rejection (3).

Through the employment of this method, researchers hope to be able to develop stem cell lines which could then be used therapeutically to treat patients specifically with their own stem cells. This research has been labelled as Therapeutic Cloning (in contrast to that of Reproductive Cloning) because the cloned embryo is made solely to obtain embryonic stem cells for research or therapy (3).

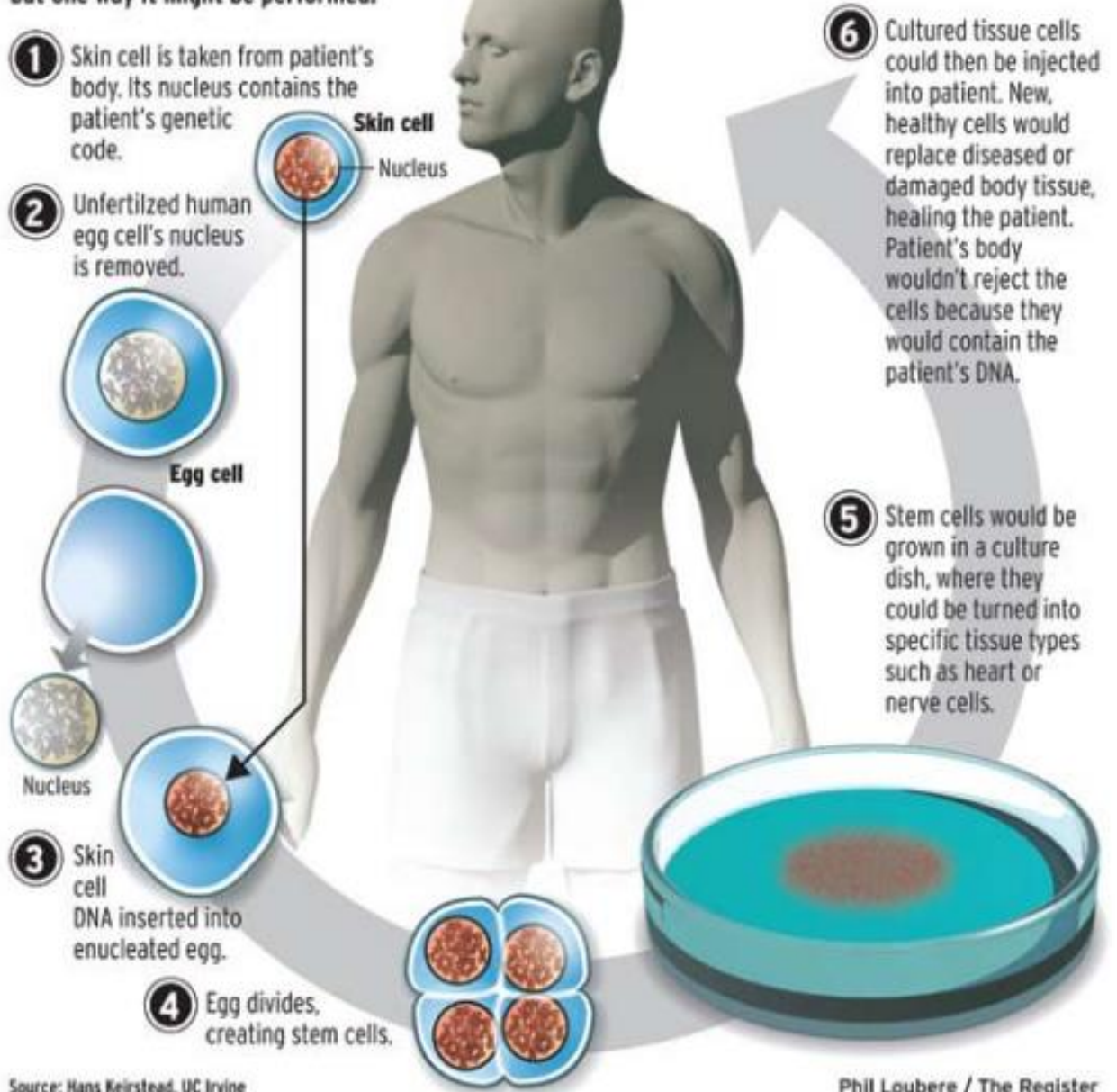
As exciting as this venture might be, scientists have yet to perfect this method with human tissue, despite a fraudulent claim by Hwang Woo Suk in 2004 (3) that he had managed to do so.

While SCNT can be described as a form of asexual reproduction, which many organisms utilise, the new embryonic cell is never implanted into a womb, human or otherwise, and brought to term. Ethically speaking doing so would be perceived as being obscenely immoral and biologically wrong, as this would change the exercise from therapeutic cloning, where patient specific stem cells are being harnessed for science or medicine, to reproductive cloning which many view as an extremely slippery slope to pursue (8). This slippery slope is based on a number of concerns, including possible threats to human diversity, health risks for clones, the problematic establishment of moral status and rights, the effect clones may have on natural human dignity and identity, as well as numerous other social implications which due to the scope of this study we are unable to further explore.

Figure 6: How Therapeutic Cloning Could Work (5)

How therapeutic cloning could work

Cloning human tissue has never been done, but one way it might be performed:



With the increased awareness of the need to find alternative sources of human embryonic stem cells, researchers are not far from perfecting this process. Nonetheless, there exists one major ethical objection to the perusal of this method, namely the means needed to acquire a sufficient amount of eggs needed to achieve any kind of impact.

The Commercialisation of Egg Donation

Due to the inefficiency of this technique, therapeutic cloning requires a vast supply of human eggs until the technique can be perfected. As this is yet to be the case, the main issue of SCNT is that relying on voluntary egg donations alone would not produce a sufficient amount of eggs needed for this cause. A legitimate concern is highlighted by J.R. Meyer (8) concerning the likely occurrence of unregulated and intensive hormone treatment as well as ovary stimulation which might expose those who choose to go through with the procedure to serious health risks and exploitation (8, 10). De Melo-Martin explores the topic of IVF practises, paying special attention to the risks women would be taking on if an associated moral obligation was placed upon them to supply medical science with eggs (29).

However the health risks posed are not the only ethical issues preventing full endorsement of this method. Another ethical issue links in with an issue of social justice. A common perception is that in order to meet the demand for eggs, the act of supplying eggs might need to be monetarily endorsed. It is cautioned that such commercialisation could lead to the exploitation of emotionally and/or financially vulnerable women (3).

In this case, that which should be a voluntary *altruistic* donation for research purposes could potentially be transformed into a coercive situation resulting in those who are economically disadvantaged in society being exploited for the potential benefit of the more economically stable populace, i.e. the stem cells of the less disadvantaged are used by those who can afford such health technologies and not by the donors themselves.

Education and level of literacy play an important role in determining whether a person is able to get a job. Being poor, uneducated and illiterate can, and does, force many women to sell their bodies (30).

With the advent of payment for female eggs, this commercialisation may cheapen the innate dignity of the bodies of these women who know no better than to partake in a degrading and inhumane exercise (8).

A feminist interpretation of this ethical issue is that the choice to undergo hormone treatment resulting in the production of eggs as well as payment in lieu of these eggs, is solely the choice of the woman herself. It is her personal autonomous decision to do with her body as she sees fit. It is argued that by consenting to such an agreement, a woman is exercising her personal autonomy and thus her bodily integrity must be respected by allowing her to make this decision. In the opinion of the author, this is quite a Western interpretation of autonomy whereby the emphasis is placed on the woman's ability to decide for herself. In some Eastern cultures, the decision to consent to such acts is not solely up to the individual, but takes into account the familial involvement as a whole. (ref, me essay East v West).

It has been argued that by paying women to donate their eggs, commercialisation of the human body occurs by placing a monetary value on specific tissues and body parts (8). Ethically speaking this is in direct conflict with the Kantian maxim which emphasises the immorality of treating another human being as a means to an end, rather than a means in and of herself.

Conversely, it has also been argued that it is only fair that women should be paid for their bodily donations; it is expanded that as it is normal practice to compensate those who take part in research trials, be it through financial gain or benefits in kind (3), then relatively speaking the same should be the case for women who undertake the risks associated with egg donations. An essential question that needs to be asked is whether it is possible to find a 'fair price' which one can pay a woman to adequately compensate her for the risks, time and productive of same?

As Jennifer Parks notes, with reference to the surrogacy industry, "reproductive tourism may lead to a 'race to the bottom' in which the countries with the most permissive reproductive laws fight one another by cutting prices in order to compete for the business of reproductive tourists" (30).

The same argument could be levelled against commercialising egg donation; although the time frame is a lot less in length than gestational surrogacy, the risks are just as high and if anything more frequent.

Creating in Order to Destroy

In an attempt to circumvent the ethical problems associated with SCNT, a new technique was proposed by William Hurlbut called Altered Nuclear Transfer. In this technique, a gene within the somatic cell's nucleus, which is necessary for implantation to occur, is 'deactivated' or genetically modified so that it is 'turned off' (3). Once this has occurred, the nucleus is transferred into the enucleated egg cell. Due to the genetic manipulation the new cell is now referred to as a *Biological Artefact* as it has been brought into existence with a genetic structure which is insufficient to generate a human embryo (10). The definition of 'Biological Artefact' should cause one to pause; the author claims that within the article referenced, the term was not fully explored and so the characteristics of what makes the modified embryonic cell a biological artefact instead of an embryo were not clarified. Such clarification is of the utmost importance both ethically and legally, especially when in relation to embryonic research and procurement.

In the unlikely event that this 'artefact', which resembles an embryo cell, is implanted into a womb the new embryonic-like-cell will **not** be able to implant and so will never be able to develop. Thus, one could argue that the ethical controversy surrounding the right to life debate has been resolved; that because this embryo-like cell lacks even the capacity to develop, it cannot be ascribed the personhood of which embryonic development plays such an important role.

Opponents of creating embryos solely for research purposes are in stark disagreement with this 'ethical resolution'. It has been queried whether the claim Hurlbut proposes - that no embryo creation or destruction takes place - has an actual basis. It is not the production of a non-human entity which causes this worry but the possibility that in this instance the deliberate creation of a doomed or disabled embryo occurs.

As explored above, it is the *intent* which the researchers employ with makes the act immoral. Thus, the intentional maiming of what could be a viable embryo is viewed as morally **worse** than if researchers were to use a surplus embryo.

Scientifically speaking, this alternative method has sparked warnings from the medical community as currently it is unknown if the genetic modification effects the productivity and proliferation capacity of the resulting stem cell lines.

Which Cell has the Right to Life?

A central criticism aimed at Single Cell Blastomere Extraction is based on the premise that, through extraction of a base cell of an embryo, i.e. one of the first divisions, the extracted cell might share the Totipotency of the initial zygote. Thus, the whole controversy of right to life could be reset but this time in defending the rights of the newly produced *Totipotent* cell (10). If the new embryonic cell has the capacity to differentiate into all other types of cells which make up a human organism, indeed if it can develop into an organism, the rights of this new kind of asexually produced being will need to be addressed as well. It can be said therefore that this alternative method does not in fact bypass the ethical concerns raised by the normative method of obtaining human embryonic stem cells.

5.4 Unethically Obtained Research

Another issue relating to consent is one which advocates that if an embryo is to be considered as a fully-fledged human person then it may be argued that no consent is given to the researchers by the embryo to carry out the invasive, life threatening procedure. This is one of the stronger arguments which should cause many advocates of human embryonic stem cell research to pause.

With the atrocious treatment of the victims of the Holocaust experiments still fresh in the world's medical history, as well as the crowning achievement of ethical error through the Tuskegee Syphilis experiments, the weight of being equated, even partially, to a Nazi Doctor appears to be a turning point for many. Can it be argued that using research results which were obtained through immoral, sometimes even repugnantly evil, experimentation is unethical?

A vast amount of controversial debate stemmed when the decision was made to use the results of the barbaric experiments performed by the Nazi Doctors. Similarly, there are some who view utilising the results of human embryonic stem cell research to be unethical and based upon a fallacy which endorses the view that as an embryo does not have the capacity or even the capability to consent, the consent is not required or invalid.

The author suggests that if this view were to be applied to incapacitated adults, i.e. those who lack the capacity, rationality, consciousness, *etc.* which according to those who subscribe to the cognitive definition of personhood shows personal autonomy is present, the result would be moral uproar. Does a deciding difference exist between these two groups? A key component of the argument to protect these groups is their **vulnerability**. Many understand and advocate that even though these individuals may not have the ability to defend themselves, safeguards need be put in place to ensure that they are not exploited by others who view them merely as bodies ready to be harvested for scientific gain (31). The point could be argued that this was the rationale behind the production of the many versions of human research guidelines as well as human rights doctrines which are enshrined in law all around the world today (31).

Hence, the argument can and has been made that although embryos appear less than human, they are in fact deserving of the same protections which are put in place for the living, vulnerable groups of society. These protections, guidelines, as well as the definitions which uphold them will be explored with more scrutiny in the following chapters.

The Ethical issues outlined above have helped to illuminate the difficulty and elusiveness which characterises the human embryonic stem cell debate. It is only through comparison to the above ethical issues where an honest appraisal of whether induced pluripotent stem cell research is capable of resolving same.

6. Does Induced Pluripotent Stem Cell Research Resolve the Ethical Issues of Human Embryonic Stem Cell Research?

This chapter aims to clarify if the introduction of an alternative method of obtaining stem cells, namely induced pluripotency, alleviates the ethical issues raised through human embryonic stem cells research.

6.1 The Beginning of Life

Where moral activists seek to protect the vulnerable life of an unborn foetus, medical researchers appear to have found a way to circumvent the moral objections of stem cell research by inducing pluripotency in somatic cells. Rather than endangering, or destroying the life of an embryo, be it donated or created, this method of obtaining embryonic-like stem cells appears to resolve many of the issues which opponents of human embryonic stem cell research opine.

Religious Influences

In relation to the religious influences which in more instances than not heavily impact the permissibility of human embryonic stem cell research, the induced pluripotent stem cell method appears to help alleviate the moral problems associated with such perspectives. This is primarily due to the fact that method of obtaining iPS cells *technically* does not necessitate the destruction of an embryo. Thus, whether or not religious influence impacts individual perceptions of this alternative method seem superfluous as the main qualm religious believers hold against human embryonic stem cell research is the supposed immoral destruction of an embryo.

That said, a technicality arises when a kind of *reductio* (14) argument is advanced, whereby due to the pluripotency of said iPS cells it may be proposed that *any and all* somatic cells which are reprogrammed to become embryonic-like stem cells are in fact embryonic cells (14). In turn it appears as if pursuing the induced pluripotent stem cell technique is redundant and does not in fact resolve the moral dilemma of whether an embryo, or embryo-like cell, deserves protection.

This line of reasoning has been described by many as fallacious, to say the least; it is imperative that the difference between embryonic cells and embryonic-**like**-cells is emphasised otherwise a danger exists whereby no alternative method of obtaining embryonic-like-stem-cells will be deemed ethical.

One may question here if a difference exists at all? If the latter is as potent in its ability to differentiate as well as proliferate, *does a difference exist?* Soren Holm had already affirmed a difference between embryonic cells and embryonic stem cells, emphasising that embryonic stem cells are those which are **derived** from embryonic cells and which are not embryonic cells in their own right (14). By extension, it can be argued that somatic cells which are reprogrammed to become induced pluripotent cells which are not identical to embryonic stem cells (8) and are far enough removed from an embryonic entity to deem any argument or link to embryonic destruction weak and nonsensical.

Definitions and Interpretations

With the introduction of induced pluripotency the ambiguous terms employed within the beginning of life aspect of the stem cell debate possess less of an impact on the morality of utilising stem cell technology. Use of elusive terms such as 'personhood' and 'person' appear somewhat out of context when applied to somatic cells which have been reprogrammed through the use of biological factors to become pluripotent. One of the major issues which may come to pass in this respect would be the legal definition of the reprogrammed cells, i.e. if the cells are capable of being reprogrammed to sex cells, are they to be afforded the same rights and protections as embryos or sex cells, or are they to be treated in a similar fashion to organs which, although they potentially may save a life, do not constitute as a life by themselves?

As explored above, more research is needed to elaborate on the distinguishing differences between what constitutes as a 'Biological Artefact' in opposition to a living body which requires legal and moral protection. This aspect of distinguishing between basic cells and living cells receives further scrutiny in chapter seven, within the legal parameters of the debate.

Potentiality Argument

The issue of potentiality is not unique to induced pluripotent stem cells, indeed it has plagued the debate of human embryonic stem cell research for decades. As the issue of potentiality in the human embryonic stem cell argument is based upon the premise that a human person is being destroyed, the issue of potentiality in this respect within induced pluripotent stem cell research is less problematic. Indeed, proponents of induced pluripotent stem cell technology argue that although the potential exists for somatic cells to be reprogrammed to become sex cells, or even an embryonic cell, there is no reason to believe that every case of induced pluripotency will result in the creation of such cells. Certainly, the entire point of exploring a different method of obtaining stem cells through induced pluripotency was to circumvent the ethical issues which stem from the existence of an embryonic entity or stem cells created from this entity. Thus the existence of the potentiality argument, especially in relation to utilising somatic cells within induced pluripotent stem cell research, does not provide a stable foundation to limit research into this valuable area of medical insight.

Through this analysis of the impact of induced pluripotent stem cell research it appears as if it undeniably resolves many of the ethical issues in relation to the beginning of life. Nonetheless, other ethical issues in relation to alternative methods of obtaining human embryonic stem cells exist, especially in relation to the social implications these create, and these need to be balanced against the discovery of induced pluripotent stem cell technology.

6.2 Alternative Sources of Human Embryonic Stem Cells

With the advent of induced pluripotent stem cells the search for other alternative sources of embryonic stem cells has slowed somewhat. This is mainly due to the diverse and complicated social problems which such alternative sources may create, and which induced pluripotent stem cells appear to sidestep.

IVF - In Vitro Surplus / Supernumerary Embryos

The new alternative use of inducing pluripotency helps to settle the social and ethical issues caused by the practise of producing supernumerary embryos.

Where the possibility that couples undergoing IVF treatment were potentially being manipulated and harnessed for their embryos, the introduction of a viable, possibly infinite, source of pluripotent stem cells via induced pluripotency, redirects the focus of scientific research away from the need to harvest unwanted or spare embryos and forces it to focus its energy instead on the less controversial and more economically viable induced pluripotent stem cells (30). The sole problem with this claim however, would be that the method of induced pluripotency has yet to be perfected and thus the use of supernumerary embryos might continue until this occurs.

Somatic Cell Nucleus Transfer - SCNT

One of the main controversial ethical and social issues in relation to SCNT is the necessity for a vast supply of eggs (ova) in order for any significant impact to take place. Primarily harvested from IVF centres, where female counterparts produced more than was needed for a successful implantation, the SCNT procedure has been documented as being extremely inefficient, with a 7% success rate (8). It is due to this staggeringly low success rate that an innumerable supply of oocytes is needed. However, the altruistic donation of human oocytes appears to fail to reach the quota which SCNT requires in order to provide some form of fruitful outcome. Thus, the possibility of a monetary incentive in order to meet demand may be utilised in various countries, for example India or Mexico where commercialisation of the human body has already begun (30). It has been cautioned that such commercialisation could lead to the exploitation of emotionally and/or financially vulnerable women.

With the establishment of a safe and more efficient method of obtaining pluripotent stem cells, which are similar to that of embryonic stem cells, it appears as if such monetary enticement of emotionally and/or financially vulnerable women is not necessary. As induced pluripotency appears to only require somatic cells, or cells which are extremely easy to obtain (e.g. hair or skin cells), not only does it bypass the above issue of commercialisation and the possible dehumanisation linked with such monetary stimuli, it in fact appears more financially viable than that of SCNT as well (8).

Due to its simplicity of production, the redundancy of commercialisation as well as its higher efficiency rate, it appears as if induced pluripotent stem cell research is better suited to large scale implementation than that of SCNT and so resolves its ethical and social issues (8).

Altered Nuclear Transfer - ANT

In an attempt to circumvent the ethical problems associated with SCNT, a new technique was proposed by William Hurlbut called Altered Nuclear Transfer. In this technique, a gene within the somatic cell's nucleus, which is necessary for implantation to occur, is 'deactivated' or genetically modified so that it is 'turned off' (3). The central ethical issue aimed at this method is that rather than solving the ethical dilemmas posed by employing SCNT, ANT actually appears to create an even more problematic ethical problem; namely the deliberate creation of a doomed or debilitated embryo (10). As explored previously in many cases it is the intent behind an act which deems it ethical or not, and in the case of ANT it has been found that the very idea of manipulating a potential embryo by inserting something destructive into the genome, even for a good cause, is morally and aesthetically offensive (10). The central ethical fear in relation to this method would be that once medical research starts down the road of deliberately engineering artificial entities with some human properties, the line between what is ethically acceptable and what is not will become significantly blurred (10).

As with the above ethical issues aimed at utilising embryos, even those which may be described as debilitated or doomed to die, the new technique of inducing pluripotency seems to circumvent these dilemmas and render ANT obsolete (8).

6.3 Ethically Obtained Research

As the induced pluripotent stem cell technique simply requires a somatic cell as a starting point, be it from a human of any age (but generally an adult) the ethical qualms of obtaining consent appear less urgent than in the case of obtaining stem cells from an embryo.

However, the author notes that perhaps it is because of the ease of being able to obtain one's somatic cells (a human being on average sheds about 30,000 to 40,000 skin cells *per hour*) that more stringent consent protocols are required. The issue of consent is more thoroughly explored within the legal issues chapter below.

Through the above exploration of the impact of induced pluripotent stem cell technology in the search for alternative sources of human embryonic stem cells, it becomes apparent that it does, to some extent, resolve the ethical and social issues associated with said alternative sources of human embryonic stem cells. Nevertheless, if the full ethical ramifications of this area are to be explored then it is imperative to understand that as the induced pluripotent stem cell technique is only in the primary levels of development, it poses its own ethical and social issues which require further discussion.

6.4 The Ethical Issues of Induced Pluripotent Stem Cell Research

Unwanted Outcomes

Even though the main contributory transcription factors needed to create induced pluripotent stem cells have been identified, little is known concerning any future repercussions of their employment. Of primary import is that expression of these factors within the fibroblast could possibly lead to tumour formation (3). The most problematic of Yamanaka's factors causing tumour genesis is the c-Myc factor, which has been associated with some forms of human cancer (3, 4). Within the study pursued by Yamanaka and his team about 20% of mice derived from iPS cells created using retroviruses developed tumours (8). That said, this factor may be removed from the process, with the outcome of an embryonic-like stem cell still expected albeit with a reduction in the efficiency of de-differentiation (4).

As well as this, the delivery method of these transcription factors also plays a major part in the resulting stem cell formation. The immediate safety concern about this approach is the integration of the viral DNA, which could potentially result in varied differentiation potential or the possibility of other malignant transformations (7).

It has since been established that transient expression of the key transcription factors by adenoviral vectors can also induce induced pluripotent stem cells, while the trans-genes will not integrate into the host genome, thereby reducing unwanted and unstable outcomes.

Where Yamanaka and Thomson employ retroviral and lentiviral systems, respectively, each system has its own advantages and disadvantages as follows: (16)

Table 2: Methods for Reprogramming Somatic Cells to iPS cells

Vector Type	Cell Types	Advantages	Disadvantages
Retroviral	Fibroblasts, neural stem cells, stomach cells, liver cells, keratinocytes, amniotic cells, blood cells and adipose cells	Reasonably efficient	Genomic integration, incomplete proviral silencing and slow kinetics
Lentiviral	Fibroblasts and keratinocytes	Reasonably efficient and transduces dividing and non-dividing cells	Genomic integration and incomplete proviral silencing
Inducible Lentiviral	Fibroblasts, β cells, keratinocytes, blood cells and melanocytes	Reasonably efficient and allows controlled expression of factors	Genomic integration and requirement for transactivator expression
Adenoviral	Fibroblasts and liver cells	No genomic integration	Low efficiency

Problems of tumour genesis aside, the efficiency of converting somatic cells to iPS cells is still relatively low, meaning that while the possibilities seem endless, their achievement might be further away than anticipated (17).

In an attempt to circumvent this problem, researchers have attempted to use cells which are more specifically differentiated in the first place, i.e. kidney cells, to create iPS cells.

It has been found in some cases that human hair cells appear to de-differentiate at a faster rate and possess more potency than human somatic cells (11). However, through their analysis it was found not only that specialist cells are harder to de-differentiate (12) but also that there seems to be more than just a barrier of reprogramming halting their progress; known as Epigenetic Memory, the de-differentiated cells seem to conserve some of their 'memory' of what their purpose was prior to de-differentiation thereby limiting the new application of the iPS cell (4, 32). The author recommends that further research is needed to overcome this barrier before the advent of clinical human trials.

Until a more stable method of expressing the necessary transcription factors is developed both to halt the formation of tumours as well as to increase efficiency, induced pluripotency will be restricted in its scope and human application will remain a far off possibility.

Justice

A central ethical issue of induced pluripotent stem cell technology is in relation to the possibility of personalised stem cell lines for each individual the world over. As mentioned above a primary motivating factor for the development and research into stem cells (and by extension induced pluripotent stem cells) is the possibility of one day being able to produce stem cells on a mass scale but in an individual capacity, i.e. each person could theoretically have their own stem cell line in a stem cell bank, perhaps waiting in stand-by for when it is needed. While the theory behind such a claim is admirable, in a more grounded understanding of the current world climate with regards to healthcare availability and cost, such a feat can be described as physically unobtainable (4).

Due to this, Yamanaka as well as Taylor et al. (4) put forward the idea of creating international and national banks of HLA-typed human induced pluripotent stem cell lines, i.e. international and national banks of induced pluripotent stem cell lines created specifically to replicate the antigen proteins of different groups in the population.

With the advent of such banks, it will not be necessary to create an individualised stem cell line per person, as "generic" stem cells will hypothetically be readily available to all who need it.

As well as this, through the establishment of these banks the cost of obtaining stem cells may be reduced (4) as it could very well be argued that such a product should be funded through the healthcare operations of each state. In the opinion of the author, social ramifications of this may have wide ranging ramifications for those countries which are not currently able to provide basic healthcare never mind semi-personalised stem cells for each individual HLA-typed group in their populations.

The method of inducing pluripotency in somatic cells appears to help resolve or alleviate the main controversial aspects of human embryonic stem cell research and application, namely the destruction of viable embryos as well as alternative methods of obtaining same. Nonetheless, it need be noted that induced pluripotent stem cell technology triggers its own ethical dilemmas, which in turn would seem to complicate rather than simplify the original aims of establishing a morally acceptable means of obtaining pluripotent stem cells. Even so, all new technologies carry with them ethical ramifications and as the induced pluripotent stem cell method is still very much in early development and modification, it can be assumed that such complications will be resolved themselves in the years to come.

Some of these complications are directly in relation to restrictive stem cell laws which vary significantly from country to country. As induced pluripotency has only recently established itself as a viable alternative method to human embryonic stem cell research in the last decade, a vast amount of current legislation concerned with stem cell regulation and policy fails to recognise this new method.

Therefore it is essential that the current foundation of stem cell regulation and law, even if only in relation to human embryonic stem cell research, is extensively analysed for weaknesses or ambiguity so that prospective alternative methods of obtaining stem cells, including induced pluripotent stem cell research, are governed by regulations which are both robust and clear in nature.

7. Legal Issues of Human Embryonic Stem Cell Research

Legal regulations and guidelines in each country around the world are influenced by numerous factors ranging from the dominant religious beliefs the country holds to whether it is a member of a congregation of states e.g. the European Union or the United Nations. While many countries enjoy a more liberal legal interpretation in relation to bioethics and human embryonic stem cell research (3), there are some which remain steadfast in their traditional beliefs who remain as yet unconvinced that the potential benefits of this medical technology outweigh the moral dilemmas it poses. The legal issues within this area of research are intimately linked to the ethical controversies highlighted in the previous chapters. Although efforts are made within the legal sphere to separate personal moral convictions from civil matters, due to the extremely recent and unfamiliar nature of the cases which stem cell technology and research presents, legal interpreters have little to no precedents on which to base any kind of guidelines or regulation. Hence it is understandable that judgements and legal implementations are unique in individual countries, to some degree. This chapter seeks to explore the various legal instruments from developed countries around the world in relation to human embryonic stem cells, the legal definitions enshrined or purposefully excluded within these, namely the definition of 'person', current guidelines on the patentability of human embryonic stem cells, as well as the legal parameters in relation to the concept of consent.

7.1 Current Legal Guidelines and Legislation on Stem Cells

Medical breakthroughs in relation to stem cell research are becoming more frequent due to the exponential progress made in the last decade within this field. Although these discoveries may be informing further research, the author notes that regulation is approaching a point where it is unable to keep up, or is found lacking. In such a field as stem cell research, where the controversial definitions as well as cultural influences become deciding factors, clear and concise, legally binding regulations have been called for (33).

An appraisal of the divergent legal positions of countries around the world serves as an attempt to elucidate this grey area of the stem cell debate, and is located in Appendix 2 of this thesis (7).

This analysis of the various global stem cell laws clearly illustrates the amount of diverging regulations which exist amongst countries from Europe, America and Asia. A world map which reflects the current policies adopted by different countries can be found in Appendix 3 of this thesis, which may further aid the reader in understanding the divergence between countries on this important topic.

Where some countries outright prohibit any kind of research on human embryos, for example Lithuania, Germany and France, other countries have authorised it albeit with some strict conditions which need to be fulfilled, for example the UK, Spain, and Italy. These conditions depend on each country's laws and ultimately are shaped by the political and social climate of each government.

In France, for example, the use of human embryos and embryonic stem cells is prohibited unless the following specific conditions are met (7):

- That the research is scientifically relevant
- That the research is likely to allow major medical advances
- That it has been expressly established that the research cannot be performed unless cells derived from embryos are used
- That the research project respects French ethical principles for research on embryos and embryonic stem cell lines (7).

Similarly in the UK, although human embryonic stem cell research is authorised subject to a licence from HEFA, any such research is strictly regulated and only permitted when the following conditions are met, such as:

- The HFEA is completely satisfied that any proposed use of embryos is absolutely necessary in order to achieve the purposes of the research (7)
- The research can only take place on embryos which have developed from eggs *outside* the body, i.e. *in vitro* embryos
- This research can only take place on embryos up to 14 days old

The above conditions can be argued to exist although to differing degrees in most policies employed by other countries, the majority of which are based in Europe (7).

Germany, for example, has a very restrictive regulatory framework in comparison to other EU countries. Under the Embryo Protection Act 1991, the derivation of an embryonic stem cell line is a criminal offence. The Basic Law of Germany also affirms that everyone has the right to life, which appears to have been interpreted as meaning embryos as well, although The Basic Law does not elaborate further on the meaning ascribed to the word "everyone". German Law, like the majority of EU countries, gives priority to adult stem cell research. While the 2002 Stem Cell Act permitted adult stem cell research, it had a strict importation of human embryonic stem cell lines regulation which included a cut-off date in relation to when said stem cell lines were established. The initial date proposed was 1st January 2002, but this was then pushed to 1st May 2007, as a result of pressure from German researchers and scientists. This cut-off date stipulated that any human embryonic stem cell lines which are created after 1st May 2007 are prohibited from being imported and used for research purposes (7). In an attempt to further protect and respect the life of the unborn, in 2006 Germany pushed for a ban on all embryonic stem cell research in the EU. However due to the divergence of culture, history, government, and regulation, an EU-wide blanket ban would not be possible, in the same way that an EU-wide authorisation of such research would also not be possible. Other countries, however have less rigid regulations and are more open to the potential such research harnesses.

With a comprehensive regulatory framework, Spain appears to have a more lenient stem cell regulation, allowing stem cell research both for research purposes as well as therapeutic application. The Law on Biomedical Research (Law 14/2007) is the leading regulation on this matter. It prohibits the creation of human embryos (and pre-embryos) which would be used exclusively for experimentation.

That said, the law allows the collection of human embryonic stem cells from pre-embryos or embryos based on the condition that the embryos are not solely created for this purpose (7).

Having such an inclusive regulatory framework has placed Spain in a strong position with regards to furthering scientific knowledge and application of stem cells.

In contrast, the United States appears to have had a very conservative approach to stem cells. The Roe v. Wade case, which legalised abortion in the US in 1973 as well as developments occurring in England around that time prompted the federal government to create a regulation which banned any form of federal funding for research which would experiment on human embryos (34). Two decades later, in 1995, the US congress passed the Dickey Amendment, which was part of an appropriations bill. The Dickey Amendment was more specific than previous regulation in the area of experimentation on human embryos; it authoritatively prohibited the creation or destruction of human embryos for research purposes. This bill was passed prior to the establishment of the first human embryonic stem cell line. Due to this, the Dickey-Wicker Amendment did not detail the precise definitions of what constituted a human embryo. This became apparent once human embryonic stem cell lines began to be established in the late nineties; in 1998 James Thompson of Wisconsin University sought to clarify that the National Institute for Health (NIH) could in fact fund any research which was conducted using stem cells obtained from these lines. Thompson opined that stem cells obtained from these lines were not human embryos according to the statutory definition and thus researchers were eligible for federal funding as no embryo were being created or destroyed. While President Clinton thoroughly endorsed this interpretation, between 2001 and 2006 President George Bush signed an executive order which restricted any kind of federal funding for human embryonic stem cell research. This restriction limited funding by only granting it to those who utilised stem cells obtained from stem cell lines already established prior to August 2001.

Due to the restriction of funding, stem cell research in the US during the early 2000s did not flourish at the same rate as other countries which had more lenient funding systems, for example, the UK. However, in 2009 President Barack Obama signed a different executive order which reversed federal opposition to stem cell research (35).

It can be a difficult scientific and ethical balance for policies to reflect the desire for progress in managing disease, but at the same time attempting to maintain the collective moral views of a nation.

Even if a country was able to create a harmonious balance between the ethical and the legal issues at play, the limits of language and its interpretations impact these regulations on a consistent basis. This is in particular due to the re-defining and development of terms as research exponentially progresses.

7.2 Legal Definitions and the Right to Life

As much as these laws serve to enlighten the stem cell debate, where no solid definitions are given, they can lead to confusing situations and leave loopholes waiting to be exploited. Arguably one of the key issues related to human embryonic stem cell research is the interpretation and meaning of the Right to Life.

While specific objections related to human embryonic stem cell research have yet to surface in the legal sphere for individual lawsuits (with federal or government funding of such research taking much of the limelight), certain cases where an unborn embryo's right to life has been considered have influenced the possible formation of legal precedents in this complex area. These cases are in relation to reproductive autonomy as well abortion. Intricately linked to the treatment of reproductive issues and abortion laws is the question of personhood and the disagreement over when human life begins (36) and what defines it.

In Ireland, for example, an important case *M.R. v. T.R.* (37) may have set a precedent for any future stem cell regulation which the country may develop. In this case, a husband and wife went through the process of IVF treatment; some of these embryos were stored for later use; the couple separated; the woman wanted to use some of the embryos; the man wished for them to be destroyed; the woman took the case to the High and then on to the Supreme Courts to appeal the decision. In this case, the woman employed the argument for the embryo's Right to Life and demanded that this be respected, and that she be authorised to use the embryos.

Known as the 'Frozen Embryos' case, it highlights how an important Article within the Irish Constitution, as amended by a referendum in 1983, is an accurate example of ambiguity within Irish, as well as international, regulation with regards to reproductive autonomy, and by extension, human embryonic stem cell research.

Article 40.3.3 provides : “The State acknowledges the right to life of the unborn and, with due regard to the equal right to life of the mother, guarantees in its laws to respect, and, as far as practicable, by its laws to defend and vindicate that right” (38).

The ambiguity here arises from the lack of an accompanying definition of the “unborn”. Due to this both medical researchers and legal professionals were unsure if the protection which had been accorded to the unborn could be extended to embryos currently being cryo-preserved. In 2009 the Irish Supreme Court agreed with the High Court's decision (of 2006) that embryos which are held in cryopreservation and are held outside of the womb are **not protected under the constitution** (7). Arguably this precedent could be employed (or exploited) by human embryonic stem cell scientists within Ireland to support their research which destroys the potential life of an IVF Supernumery embryo.

A different case which also highlights the need for clearer legal parameters in relation to the beginning of life, personhood and the Right to Life, is the Roe v. Wade case which took place in the United States in 1973. While this case deals with abortion, similar to the above, indirect conclusions can be derived and applied to modern human embryonic stem cell research. In this case, the issue of when human life truly begins, i.e. when an embryo acquires personhood status, came to the fore. While establishing the right to an abortion in the first trimester, the decision of the Supreme Court states the right to intervene in the second and third trimesters of pregnancy to protect the woman and the "potential" life of the unborn child. Thus the courts were demanded to pinpoint the exact time when this 'potential' life of an unborn child begins. The court deflected this appeal by employing the term 'viability'. The court outlined that the viability of an embryo determined the permissibility of abortions performed for reasons other than the protection of the woman's health.

It went on to define viability as "the point at which a foetus is potentially able to live outside the mother's womb, albeit with artificial aid" (39).

This interpretation of the viability of embryos being something directly linked to its personhood, humanity and protection, led the public to fear the possible exploitation of embryos which were younger than the age of viability and which could be aborted, used or destroyed in an unregulated and unethical way by medical science.

What this definition lacked was clarity surrounding its terms - particularly with regards to embryos which are developed in vitro for research purposes, through the use of artificial aid, which may never have the opportunity to reach the stage of being characterised as a 'foetus'.

The effect these two cases have had is to force the general public to confront those legal regulators, who have the ability to stimulate change, do to so in order to either protect the innocent interpretation of early embryonic life or to justify why this protection is not afforded. It must be noted that these court decisions were not meant to be used as a basis for stem cell research law and regulation, but the structure of law as it is in many common law countries relies on precedent and once a precedent has been set, it's difficult to challenge. This is why further clarity is needed by courts dealing with such sensitive issues as personhood, the right to life, IVF and abortion.

7.3 Legal Parameters of Consent and Confidentiality

The issue of consent, although steeped in ethical and philosophical reflections, finds its true recognition through the voice of the law. Deriving much from the Nuremberg Code as well as from the Belmont Principles, current laws relating to the donation of tissue heavily emphasise the need for explicit, **informed** consent to be given prior to any kind of medical research, operation, or process. Positions regarding research on human embryos may be even more nuanced and complex than normal medical research (40) due to the sensitive nature of the subject. *(Some have even argued that the act of donating an embryo to research accords it greater respect than the act discarding it (40)).*

The concept of consent is intimately linked with that of personal autonomy. Indeed, giving one's consent to an act, or donation, is often described as an expression of personal autonomy. It may be argued, as above, that in the case of the foetus, such expression of consent is not possible. While some argue that this supports the idea that a foetus is not in fact a person, others look to the Belmont report which stipulates that "respect for the immature and the incapacitated may require protecting them as they mature or while they are incapacitated" (31). Thus it could be argued that the embryo does not give its consent, and so the destruction of its life through the process of deriving human embryonic stem cells is wrong.

This is where the idea of substitute consent forms; explored within his article *A Regulatory Argument Against human embryonic stem cell research*, Stephen Napier outlines the concept of substitute consent. He suggests that substitute consent occurs when a guardian(s) or state step in to decide what may be best for the embryo. He employs the use of a risk-benefit ratio.

The risk-benefit ratio is a ratio Napier proposes to compare the weight of risks versus the weight of possible benefits of an act. Generally an act is deemed permissible if the benefits outweigh the risks. The ratio finds expression more so in circumstances where an individual or group are unable to provide informed consent, most likely due to their vulnerable nature. The risk-benefit ratio takes into account the risks associated with the research and through a process of extension and application to the test subject's position, evaluates whether consent, and the degree of it, is required. For example, even if autonomous subjects give their consent, a risky research project is not ethically justifiable.

Napier applies the risk-benefit ratio to the idea of substitute consent and highlights a major problem, namely that rather than taking into account solely the risk-benefit ratio of the embryo, the one making the decision may have been unduly influenced or coerced into a specified choice which can alter what would be the 'right' decision on behalf of the embryo (31).

An example of this would be if the substitute consent is given by the genetic parents of the embryo in lieu of payment for their embryo.

Here, the risk-benefit ratio is subjective to the donating parents, and little thought is given to that of the vulnerable embryo i.e. rather than weighing the potential risks and benefits which will directly impact the embryo, the parents solely focus on their own potential benefit and proceed to put the life of the embryo at risk.

If the idea is accepted that an embryo should be considered as possessing some form of innate personhood, due to its lack of physical capabilities it can be argued that it should be considered as a vulnerable person which requires substitute consent for all procedures.

Therefore if it is exposed to greater risk than benefit through the process of human embryonic stem cell research, then it is imperative that unbiased regulations are put in place to protect vulnerable groups such as these. The more vulnerable a subject is, the greater the need to protect that subject (31).

While employment of this ratio may highlight concerns which are overlooked by medical researchers, in the opinion of the author Napier did not do the ratio justice in his explanation and rather than emphasise the need to focus on those vulnerable in society, he confused his readership with the introduction of his ratio. An alternative route which he could have employed could have been through recourse to John Rawls' A Theory of Justice, where the issue of potential vulnerability is a significant factor (41).

The Belmont Principles are one attempt to outline and implement regulations which seek to protect those who are vulnerable within society. There are three main principles which are central to the Belmont Report;

- Respect for persons: This regulation comprises of detailed stipulations for groups whom can exercise personal autonomy and choice, as well as those who are unable to exercise their autonomy.
- Beneficence: The ethic of beneficence embodies two essential characteristics of biomedical ethics, specifically, do no harm and maximise benefits.
- Principle of Justice: Stipulates that researchers must avoid selecting their test subjects on the basis on "their easy availability, their compromised position or their manipulability" (31).

Consent in relation to every day matters, such as shaking someone's hand or allowing someone to give a massage, is on a much less intense scale than the consent required for that of new and untested medical research, i.e. The kind of consent necessary for a risky medical procedure which has little or no benefit may carry greater weight due to the greater risks which the patients may be exposed to, as highlighted through the risk-benefit ratio.

There exists a wide degree of consensus about the main substantive elements of a regulatory approach. Briefly summarised the main elements of regulating human embryonic stem cell research and consent are as follows (18):

- Autonomy of the gamete and embryo donor needs to be respected at all times;
- This respect can be epitomised through the action of giving informed consent;
- This consent is only valid if it is free of untoward influence or inducement;
- Such consent is only fully informed once the donor understands:
 - The risks of the procedure to donate
 - What will happen to the embryo in derivation of ESCs
 - Alternative uses of embryos
 - That the donated material may be stored for years
 - That no restriction of who might benefit from the donation exists
 - That the research results may have commercial value, in which the donor will not share
 - That there will be no direct medical benefit to the donor
 - That information relating to the donor's identity might be retained
 - That this donated material may be employed in future, as yet unrealised, research and may be made available to use in medical procedures

As the last point highlights, the issue of informed consent within the debate of human embryonic stem cell research is not restricted to the diverse scientific understandings and developments of the current day and age. Philosophical considerations which are linked with defining legal parameters of consent have acknowledged the need to question exactly **what and to what extent** patients are consenting (to) when they donate their embryos or sex cells.

For this reason the HFEA's Code of Practice for IVF clinics highlights to those who are considering embryo donation the possibility that any stem cell lines which are created may continue indefinitely and may be used in different research projects (42). This is an important element for governments to consider when regulating stem cell research. It can be argued that in the case where the far reaching possibilities of their donation are not outlined, the consent which patients give to the research is not in fact fully informed.

Although it may be impossible to accurately represent future research aims, theoretically donors could consent to general areas of research which they feel comfortable that their donations are being used for (40).

An interesting case of note in regard to consent and the use of donated material is that of Henrietta Lacks. Henrietta was the unwitting source of cells which were cultured by George Otto Gey to create the first immortal cell line for medical research. These cells were derived from the cancer cells of Henrietta's tumour. Gey named the sample HeLa. Due to the immortal nature, i.e. the ability to continually multiply without loss of potency, Henrietta lacks' cells were used internationally for numerous experiments.

Although the far reaching effects of this research stirred something of an exponential growth in medical and scientific research, neither Henrietta nor her family gave consent for her cells to be employed in such a way. It can be argued that at the time when this case occurred (1950s), consent was not recognised as being as important as it is today. Such a case causes many to question the morality of using research which was achieved through unethical means; as has been mirrored through the controversial use of the medical findings of the Nazi Doctors obtained during WWII.

In dealing with such sensitive material as human embryonic stem cells, the author affirms that it is important for researchers to emphasise the possible future need of identifying the donor, when consent is being sought from said donor. As explored in the Henrietta Lacks case, stem cell lines may have numerous applications which we have yet to discover and may equate to the theoretical tracing of a donor (43).

Such issues of confidentiality carry a heavy weight on whether or not a person may wish to donate. Where some may affirm that the anonymity of the donors needs to be protected, lest a drop in already low donations occurs, others argue that in order for researchers to adequately prove that consent was obtained some kind of code which links a donation to a donor will need to be put in place (40).

Issues of consent aside, if certain stem cell lines are to be employed to treat patients in clinical trials, or through future therapeutic measures, identification of the donor will be needed to document appropriate screening for infectious and genetic diseases (40).

While this may impact the growing need for embryo and gamete donors, it may be imperative for researchers to employ only those donors who agree to be re-contacted in the future should more information or tests be necessary (40).

What has become apparent through the above appraisal is that the essential aspects of consent which effect human embryonic stem cell research are the voluntary nature of the donations, the full understanding of the consequences of the donations, as well as the parameters or boundaries as to what said donations are to be employed. Alongside this, the issue of confidentiality and exactly what it pertains to needs to be examined under closer scrutiny and applied to new medical breakthroughs, whereby remaining anonymous may not be possible due to the genetic link between the donor and the donated material.

7.4 Patenting Stem Cells

Patenting is a process whereby the intellectual property rights of an invention (as opposed to a discovery) are owned by a particular entity, be it a person, group or company. Thus only those who have invested in or who have obtained a patent may use or distribute their invention - usually at a high price. Patents in Europe currently last for twenty years (44), with the aim of allowing a kind of monopoly in the area of the patented invention, so that the inventor and/or investors may recoup the financial expenses devoted to the culmination of the invention.

These intellectual property rights are bestowed upon the inventor with the prerequisite that the inventor will publish the details of the invention for anyone in the world to access (44).

The debate concerning whether or not it is appropriate to patent life forms or biological material has received extensive critique and exploration for the past decade, especially in North America and Europe (3). While the patenting of adult stem cells has been accepted throughout most of Europe, albeit established through the necessity of informed consent, a disparity in opinion occurs when the debate focus shifts to the allowance of patents for embryonic stem cells, as well as the embryos they have been derived from.

The most notable guidelines in relation to this European debate are those stated in the *European Patent Convention* (45) whereby Article 53(a) notes that "inventions the publication or exploitation of which would be contrary to 'ordre public' or morality" (45) are those which are excluded from being patentable (3). A common critique of this exclusion was that the terms 'ordre public' and 'morality' received no further elucidation in the Convention and so European states seeking clarification were left to their own interpretations (46). This continued up until the 1998 *EU Directive (directive 99/44/EC) on the legal protection of biological inventions* (47) was introduced (3) in an attempt to harmonize the field of biotechnology patenting within Europe (48). This Directive declared under Article 6 that patents are not to be granted "in respect of human embryos for industrial or commercial purposes" (47) as this was contrary to morality (3). Through its incorporation into the *European Patent Convention* as Rule 23(d-e) the Directive appeared to allow the patenting of isolated elements of the human body, but only if these elements establish more than a discovery, i.e. an invention (3). This aspect of isolated elements of the human body was outlined within Article 5 of the Directive (48).

At this juncture the debate of the living cells interpretation of stem cells versus the isolated biological function interpretation of stem cells reaches its apex. Where the former upholds the belief that human embryonic stem cells are living cells and thus deserve full respect as living beings, the latter aims to interpret the cells as mere biological material, comparing these stem cells to organs or limbs i.e. lifeless but not without biological function and merit.

The differing meanings proposed by each group influence the patentability of human embryonic stem cells within each country around the world. This can be seen through the above incorporation of the *EU Directive (directive 99/44/EC)* into the European Patenting Convention, which consolidated ethics as a factor in European patenting decisions (3, 49). Where embryos as well as embryonic stem cells are perceived as representing human life in its most primary form, the granting of patents can be understood as devaluing, infringing or violating human dignity (3, 50).

However, it has been argued that the ambiguous phrasing of Article 5 in the Directive (99/44/EC) was employed in order to enable the granting of certain patents which theoretically did not clash with the Directive directly and would thus encourage research in the field of biotechnology (48). One of the ways this was done was through Article 5.1 and 5.2; namely, that (5.1) the human body, or parts thereof (for example genes occurring naturally in the human body) cannot be patented, but that (5.2) parts from the human body which have been isolated from their natural location in the body or which have been produced through synthetic means can be patented (46). This creative word play did not subdue the criticism aimed at the European Convention. In fact it caused other important issues which are linked to the allowance of patenting human biological material to be pushed into the legal and ethical limelight.

One such issue which has informed the non-permissibility of the act of patenting human embryos or their stem cells is in relation to the commodification and instrumentalisation arguments. Both the Danish and French National Ethics Councils have emphasised that premised on the principle of non-commercialisation of the human body, stem cells which have not been significantly modified should not be patentable (3). The concept of human dignity touched upon above assumes with it the innate non-instrumentalisation and non-commercialisation of the human body as well as its parts (3). Due to the fact that the possibility of patenting has a financial incentive for it to be pursued, it is feared that the existence of these patents may boost research on embryos. As the primary source of these embryos is through Supernumerary Embryos, logically there may develop an overabundance of surplus embryos being developed than would have materialized without the enticement of patenting (46).

Even though the European Patent Office seeks a balance between what is ethically moral and scientifically feasible, the European Molecular Biology Organisation has implored the EPO to reconsider its current standing in relation to the patentability of human embryonic stem cells and embryos. The reasons for this are related to the competitive nature of stem cell research, as well as the economic and health care benefits which may be accrued from such research (3).

On the flip side of the same coin, by issuing patents to companies which aim to primarily invest in this area of research, small biological companies who cannot afford to pay research licenses to these patent overlords will struggle and thus research may be stifled (3). Such research barriers have the potential to create obstacles to medical development of procedures and products which may have significant benefit. Due to this many bioethics councils of Europe have urged the EPO to refrain from granting overgenerous patents with broad claims (3, 43, 46, 50).

8. Does Induced Pluripotent Stem Cell Research Resolve the Legal Issues of Human Embryonic Stem Cell research?

As induced pluripotency has only recently established itself as an alternative method to human embryonic stem cell research in the last decade, a vast amount of current legislation concerned with stem cell regulation and policy fails to fully elucidate and guide this new practise. As such, this leaves areas of this particular method open to exploitation and misuse. While current stem cell legislation has been highlighted in the previous section, this chapter will be dedicated to exploring whether the introduction of induced pluripotent stem cell technology has in some way or another improved the legal situation. In order to be concise as well as clear in exploring this question, the below appraisal will aim to identify how this new mechanism of obtaining stem cells effects the legal matters highlighted in the previous chapter.

8.1 Current Legislation

Due to the situation of both heightened scientific expectations and ethical tensions in relation to stem cell research, countries all over the world have developed differing policies as well as regulations. This concept of ambiguity was explored in the previous chapter, and while the uniting front of many of these policies was the declaration that no embryo should be created or destroyed specifically for research purposes, the uncertainty and questionable regulations governing stem cells seems not to have been effected as drastically as that of the ethical issues raised by human embryonic stem cell research. This is highly likely to change within the coming years as induced pluripotent methods develop and a decrease in the demand for stem cells derived from human embryos occurs. However, many hold that even with the advent of such a promising technology, induced pluripotent stem cell research will still require human embryonic stem cells in order to control and cross reference any achievements and to regulate the safety of these cells.

8.2 Legal Definitions and Interpretations

The predominant focus of this avenue of the stem cell debate is in relation to the definitions and interpretations attached to the terms surrounding early human life, namely 'embryo', 'baby', 'right to life', and 'unborn'.

As the method of inducing pluripotency within somatic cells does not utilise the life of an unborn embryo, be it created, donated or discard, one would surmise that this avenue of legal ambiguity has finally been resolved. Unfortunately, this does not seem to be the case. In September 2013, a team based in Spain published a puzzling article in *Nature* (51), where they reported being able to cultivate iPS cells *in vivo* by employing the same techniques as applied to cultivating iPS cells *in vitro*. The main question here would be is there really that much of a difference between the products of this comparison? Startlingly, yes there is! The essential conclusion drawn by this team was that the induced pluripotent cells which were cultivated *in vivo* appeared **extremely similar** to embryonic stem cells, as well as being distinctly different to induced pluripotent stem cells produced *in vitro* (16).

This brings a new technical problem to the cutting edge of the stem cell debate. Where stem cells were developed *in vivo* it was found that they presented with a remarkable ability to produce embryonic-like structures (16). While this has been the epitome of what *in vitro* iPS cells were believed to be able to do, the difference in capability is striking. Where iPS cells produced *in vitro* are able to differentiate into any of the three germ layers, those cultivated *in vivo* appear to share the true capacity and potential of totipotent stem cells (16) i.e. being one step closer to the 'Golden Standard' ascribed to totipotent stem cells. Hence a conceptual problem exists; namely, the differentiation between Totipotent and Pluripotent induced stem cells. As this new discovery develops, will it still make sense to talk about pluripotent stem cells lines if in fact these lines are capable of totipotent application?

While this problem of definitions does not apply immediately to current stem cell research, the author suggests that it is a possibility that if no proper legal demarcation and definition takes place, issues such as patentability as well as quality assurance, perhaps even safety concerns, will be prone to legal and

commercial exploitation. Indeed, the need to redefine legal and ethical boundaries seems to be transforming into a constant requirement of the modern medical world (16).

8.3 Consent and Confidentiality

One of the most significant issues associated with induced pluripotent stem cell procurement and research is that of informed consent and the associated privacy of cell donors (52). Similar to the issue of patient confidentiality explored in relation to human embryonic stem cell procurement (or alternative methods of procurement), the resulting iPS cell lines which are derived and developed from an individual will possess that individual's DNA 'fingerprint' (52). A donor's sample could theoretically possess an immeasurable amount of personal information, not only in relation to the specific individual but also in relation to his/her immediate family and friends (52). Any breach of confidentiality could violate the individual's privacy and could result in economic or social risks (52). In the United States, the *Genetic Information Non-discrimination Act 2008* was established as a legislative response to these concerns. However, the extent to which legislation such as this will be able to control genetic discrimination has yet to be proven.

Social and ethical considerations which are linked with defining legal parameters of consent have acknowledged the need to question exactly **what and to what extent** patients are consenting (to) when they decide to either donate somatic cells to induced pluripotent stem cell research or, assuming it will be possible at some point in the future, when they choose to set up a personal or familial stem cell line.

As iPS cell lines become more common place in the personal medical sphere, perhaps the consent which is obtained from donors/patients could include a paragraph similar to that found in the HFEA's Code of Practice for IVF clinics. This Code highlights to those who are considering embryo donation (or in this case cell donation) the possibility that any stem cell lines which are created may continue indefinitely and may be used in different research projects (42).

This is an important element for governments to consider when regulating stem cell research as it can be argued that in the case where the far reaching possibilities of their donation are not outlined, the consent which patients supply to the research is not in fact fully informed. Although it may be impossible to accurately represent future research aims, theoretically donors could consent to general areas of research which they feel comfortable that their donations are being used for (40, 52).

Even if an adequate form of consent has been obtained and the process of forming a stem cell line has begun, a major aspect of personal privacy becomes apparent in the instance where an individual attempts to withdraw his/her consent. While traditional research standards require that an individual is able to withdraw his/her consent from research at any point, within human embryonic stem cell research (and by extension induced pluripotent stem cell research) exceptions to this rule appear to be the norm (52). One particular guide states that donors are only able to withdraw their consent until the creation of the stem cell line has taken place (52). Even if an individual decides to withdraw consent, in many circumstances depending on how the cell line has been used and in what jurisdictions it may be near to impossible for complete withdrawal of donor consent to occur (52).

Such issues of confidentiality may constitute a major aspect on whether or not a person may wish to donate cells or establish a stem cell line. A popular suggestion which attempts to address these concerns would be to anonymise the data at the time of donation (52). However due to clinical, research and policy reasons the method of anonymising data may not be the ideal approach. If certain stem cell lines are to be employed to treat patients in clinical trials, or through future therapeutic measures, identification of the donor will be needed to document appropriate screening for infectious and genetic diseases (56). As well as this, it is possible that future clinical applications may necessitate obtaining follow up information concerning the donor's health (52).

What has become apparent through the above appraisal is that similarly to human embryonic stem cell research, the essential aspects of consent which effect the development of iPS cell lines are the full understanding of the consequences of the donations and the parameters or boundaries as to what

said donations are to be employed. Alongside this, the issue of confidentiality and exactly what it pertains to needs to be examined under closer scrutiny and applied to new medical breakthroughs, whereby remaining anonymous may not be possible due to the genetic link between the donor and the donated material.

8.4 Induced Pluripotent Stem Cells and Patenting

Within stem cell research and ethics, the principles of protecting human dignity and integrity of the person is inscribed within European Patent Law, especially in relation to patenting and the commercialisation of inventions based on biological material (16). Patenting of human materials, and more importantly inventions which have been built upon the destruction of human embryos, was prohibited by the *Directive 98/44/EC* in 1998 due to the moral outrage caused by such acts. However, a landmark decision made by the European Court of Justice in 2011 which ruled on the Oliver Brustle vs Greenpeace case created a legal loophole for those wishing to one day patent inventions related to iPS cell research (16).

Brustle, a leading German stem cell scientist who holds a patent on neural cells produced from human embryonic stem cells, argued against the decision of the European Court which found that the *Directive 98/44/EC* extended to prohibiting the patentability of “procedures involving human embryonic stem cells or cells that are grown from human embryonic stem cells”. Brustle challenged the court’s decision by contesting that the original *Directive* did not define exactly what an ‘embryo’ is. Due to this, Brustle applied his own definition of what constitutes an embryo, which is that an embryo only comes into being 14 days after fertilisation. As he was obtaining the human embryonic stem cells from five or six day old ‘embryos’, he did not believe he was in violation of the *Directive* (53).

Brustle’s challenge failed as the Court affirmed that within the meaning of Article 6 (2) (c) of *Directive 98/44/EC* “any human ovum after fertilisation or any human ovum not fertilised but which, through the effect of the technique used to obtain it, is capable of commencing the process of development” is to be regarded as a human embryo and so **cannot be patented** (16).

An immediate ban came into effect on patents which necessitated the destruction of a human embryo in order to obtain stem cells (16). This ban included patents of inventions which utilized stem cells created through the use of surplus IVF embryos, parthenogenesis, as well as SCNT (16).

The legal loophole which was left open for those wishing to patent iPS cell inventions was in relation to the exclusion criteria advised by the Court. The way which the court formulated its ruling allowed the possibility to patent pluripotent stem cell lines as well as products derived from same (16). This occurred because the court used a strict definition of totipotency, linking it directly to human embryonic stem cells and thus specifically excluding this particular type of totipotent stem cell, i.e. an embryonic totipotent stem cell, from being patentable (16). This ruling was based upon the presumption that totipotent stem cells cannot be technologically created, i.e. through any other means other than from embryonic tissue (16). As stem cell research and technology has progressed, it appears as if researchers and scientists are getting closer to being able to produce totipotent stem cells without needing to destroy an embryo in the process. The latest findings highlighted above by the Spanish team in 2013 are case-in-point of this type of development (16).

Directly related to the permissibility of patenting biological artefacts is the issue of patient ownership, or as Scott et al. label it, the issue of Reach-through Rights (52). Within the article *iPS Cells: Mapping the Policy Issues*, Scott et al. explore the nuances of property rights in relation to those who have donated biological tissue/artefacts to researchers who have then gone on to patent and possibly profit from the exploitation of said biological materials. The central question raised here would be if any of those profits are due to the people who originally donated their biological materials?

One line of thought argues that even though the resultant iPS cell lines are genetically identical to the donor, the cells would have gone through a transition which transformed them into new and distinct products which bear little resemblance to their original composition (52). If we are to assume that the cells are so far removed from their original characterisation of 'belonging to' or 'being part of' a person, would this really limit the amount of control an individual would have in relation to the use of his/her cells?

Should donors have the right to receive financial benefit from commercial profits which result from lines derived from their donated cells? Are they able to “reach-through” to future instances where their cells are utilized and exercise this right?

In the case of Henrietta Lacks, the only form of redress her family received occurred in 2013, when the National Institute of Health (NIH) acknowledged the ethical issue of consent which had been at hand for over half a century (i.e. that Henrietta’s cells and genome were made widely accessible to the public with no form of consent from either her or her family). Consequently the NIH made an agreement with the Lacks family that only those who apply for and are granted permission to access Henrietta’s genetic data will be allowed to do so (54). The Lacks family have not, and will not, receive any financial compensation for the billions of dollars which have been generated upon the exploitation of Henrietta’s genes and cells (above). The issue of compensation however was made somewhat less important through the US Supreme Court’s decision of 2013 that naturally occurring genes could not be patented (55).

This question of whether donors retain some kind of property right in their bodily tissues or genetic data after donating it for research purposes has been dealt with in many American courts, for example the case of Greenberg vs. Miami Children’s Hospital Research Institute. This case saw Reuben Matalon (the defendant) use tissue samples which had been obtained from children from the Miami Children’s Hospital and who had Canavan Disease. Matalon went on to isolate and patent the Canavan gene sequence and subsequently developed a genetic test to screen for the disease. Due to his patent, Matalon received royalties whenever this test was used. The plaintiffs of the case, namely the parents of the children as well as three non-profit organisations who had developed a confidential Canavan Disease Registry and Database in the case, argued that the defendant had not obtained the necessary informed consent needed for the research conducted. This claim was ultimately dismissed from the court and the case went on to set the precedent for determining ownership of donating tissue samples in that its final ruling was that: individuals **do not** own their tissue samples when researchers use it for testing (56).

However, the author notes a key consideration in this area is how well the approach of the US courts complements one of the central bioethical principles, namely personal autonomy?

If medical researchers are to respect the personal autonomy of their donors, should they not also recognise the autonomy-derived right of control over tissue and health information? In two Canadian cases, *R. v. Dymment* and *McInerney v. McDonald*, the Court supported the idea that any tissue and health information “remains in a fundamental sense one’s own, for the individual to communicate or retain as he or she sees fit” (52). Even though these cases were (respectively) primarily concerned with issues of consent and release of personal information, the fact that the courts emphasised the need to respect the privacy of patients’ personal health information communicates the importance which can be attached to reach-through rights.

Bearing in mind the numerous cases (52) where the courts have both rejected (US) and upheld (Canada) the property rights of donors with regards to their donated tissue, confusion and uncertainty remain as current laws in this area vary significantly, both nationally internationally. As well as this, different philosophical approaches and cultural influences add even more complexity to the use of property rights in this context (52).

A general concern of those hoping to one day secure a patent in relation to iPS cell lines and their derivation, is that patents which are already in existence which were based on human embryonic stem cell research may already encompass such methods (52). Due to this, future interest in researching iPS cells may diminish as prospective investors would not be able to recoup any of the funds supplied to such projects. This is a significant barrier which faces iPS cell research (52). As well as this, other questions remain as to the different extents which patents can be secured. Will every new variation of the reprogramming technique result in a new patent, or does this count as an expected step which researchers were to follow and thus “unpatentable”? The same question arises if a new type of cell is reprogrammed – will this result in a new patent as well? It needs to be recognised that “the patent landscape is important, not only for efficient research progress, but also for the commercialization and clinical translation of the technologies” (52).

If too many patents are supplied in the present climate of stem cell research there may come a time where medical patents may develop into a thicket too complicated and expensive to negotiate in order to efficiently exploit the technology which was originally intended for human benefit (52).

In order for induced pluripotent stem cell research to remain as avid an interest to researchers as it currently is, the granting of overbroad patents in the present needs to be curbed. Furthermore, it may be necessary to acknowledge that current patent guidelines and regulation are not able to sufficiently match or control the pace of medical breakthroughs which are taking place in this advance field of bio-technology. Through this appraisal of the legal issues related to patenting induced pluripotent stem cells one can conclude that the advent of this technology does not adequately resolve the legal issues associated with the commercialisation of human tissue or cells which were primarily generated through the patenting of human embryonic stem cells.

9. Conclusion and Recommendations

The initial positive and beneficial expectations of stem cell research has and will continue to appeal to both the medical and scientific communities. With the possibility of discovering cures for neurological, motor, perhaps even all, diseases on the horizon, researchers as well as the public are advocating for more thorough research into the availability and production of these miracle cells. That said, numerous ethical and legal issues have acted as a barrier to such research. These have stimulated the developing ethical guidelines and restrictive legal policies which have slowed research and delivery of new and approved medical solutions.

The aim of this thesis was to establish whether the ethical and legal issues caused by human embryonic stem cells could be alleviated or resolved by the more modern alternative approach of induced pluripotent stem cells.

The appraisal of the ethical issues generated by human embryonic stem cells found that the introduction of induced pluripotent stem cells as an alternative method of obtaining stem cells would alleviate or resolve many of these issues: Key among these is that induced pluripotent stem cells do not utilise an embryo as a means of producing stem cells. Induced pluripotent stem cells usage of somatic skin cells as opposed to human embryonic stem cells is a significant factor in countering ethical debate as well as the public or scientific perception regarding previously strong positions as to the point where life begins, personhood, religious influences, the potentiality of an embryo, the associated empirical or cognitive faculties associated with the definition of person, as well as the issue of the right to life of an embryo.

In addition, employing induced pluripotency as an alternative method of obtaining embryonic-like-stem cells dispels the necessity of other alternative methods of obtaining embryonic-like stem cells for the same reason outlined above; namely, that supernumery IVF embryos are not needed to obtain stem cells; that the social issue of sourcing human eggs is unnecessary as induced pluripotency can be performed on somatic cells; and that there is no need to deliberately maim a viable embryo as there is no requirement for any kind of embryo in the first place.

In light of these findings it can be concluded that induced pluripotent stem cells alleviate or resolve the ethical debate related to the use of human embryonic stem cells.

Induced pluripotency provokes its own ethical problems. Although primarily research based, they have ethical ramifications if not adequately addressed. A significant concern of induced pluripotency is related to the specific transcription factors which are used to stimulate pluripotency within a differentiated cell. Noteworthy is the factor c-Myc which has been established as a primary contributor to the formation of tumours within stem cell experiments. The ethical ramification of this is the possibility of tumour formation in human patients when this technology becomes available to clinical trials. It is recommended that further research ought to be conducted to establish the possible ramifications of utilising different transcription factors. This research should take into account the effect on efficiency and differentiation capacity of the resulting stem cells.

Another important issue related to the induction of pluripotency is the method of inserting and activating the necessary transcription factors within a cell. As explored above, the different methods which are currently being utilised in this area of research involve the use of viral systems, namely retroviral and lentiviral. A considerable problem with the use of these systems is the possible genetic incorporation of the virus into the resulting stem cell lines, which also may cause unknown repercussions further down the line when clinical experiments in human trials begin.

The final ethical issue related to induced pluripotent stem cells is related to the social issue of justice. While part of the attraction to this method is its possible global application, this universal availability of generic stem cells in stem cell banks can be described as a pipe dream. In a climate where third world countries are struggling to address basic health problems due to the costs associated with doing so, it is highly unlikely that induced pluripotent stem cells, as well as possible cures resulting from research conducted on same, will be made available to those who inhabit these countries.

It is recommended that going forward, researchers who invest in utilising induced pluripotent stem cells in their search for treatments and cures of the world's most degenerative diseases, bear in mind the need to keep the costs of doing so down, or at the very least attempt to do so once the correct method of obtaining same has occurred.

The second half of this thesis was aimed at analysing whether induced pluripotent stem cells solved the legal dilemmas caused by human embryonic stem cells. Through the analysis it was found that the current legal context which governs stem cell research, collection and storage varies significantly from country to country. This was established as being due to the diverging cultural, social, and historical influences which are unique to each country. Hence, although the introduction of induced pluripotent stem cells does alleviate the need to legally define the point where life begins, as well as when personhood is ascribed, it does not appear to clarify the numerous legal issues related to stem cell regulation.

As one of the most important legal issues of stem cell research, the protection and respect of the embryo is not adequately resolved through the employment of induced pluripotent stem cells. This is due to the claim that it may be possible, perhaps not at the current point in time but in a few years, for scientists to create sex cells through the use of inducing pluripotency in somatic skin cells. Ethical and social ramifications of this would be that these new sex cells are to be treated as such and so are also therefore capable of becoming embryos if united. However, this appears to contradict the initial purpose of attempting to find an alternative method of creating embryonic-like-cells in the first place; namely, circumventing the ethical and legal dilemmas posed by human embryonic stem cells.

The legal issue of consent was essentially indistinguishable between human embryonic stem cells and that of induced pluripotent stem cells. This is due to the fact that the issue of consent is quite misleading when it comes to stem cells. Where consent is usually a once off necessity for a singular medical procedure, in the context of cells donated for stem cell research the consent obtained may not encompass all medical procedures which the cells may be used in.

This is because the consent given will not be limited to the initial establishment of a stem cell. In fact, the genetic blueprint of the individual remains within the stem cell line for as long as it exists and the applications of same are numerous in number. The primary issue with this is that researchers are unable to adequately inform cell donors of the possible future uses of their cells. This is due to the fact that stem cell research is still very much in its primary stages of development; i.e. it is currently unknown how many applications might be possible with these stem cells. In order to adequately address this problem, it is recommended that until researchers are able to absolutely inform donors how their cells will be utilised, a general outline of possible uses for the resulting stem cells derived from their donations should be supplied to them. From this general outline, they might be able to choose which area of research and application they would be happy for their cells to be used in.

Another major legal issue relating to stem cell research is that of patenting. Applicable to both human embryonic stem cells as well as induced pluripotent stem cells, patenting is an important aspect of scientific research. Through the analyses made within chapters six and seven, it was found that current legislation which regulates the patentability of human embryonic stem cells is strictly regulated, and in most countries banned as the patenting of these stem cells would be contrary to public morality and order. However, as is the case in Europe, the European Patenting Office will authorise the patenting of isolate elements of the human body, but only if these elements establish more than a discovery, i.e. an invention and which are not based on the destruction of a human embryo.

In this way it appears that the production of induced pluripotent stem cells may be authorised, due to the fact that the discovery and production of induced pluripotent stem cells are not based upon the destruction of a human embryo, as well as the fact that these stem cells can be described as isolated elements of the human body. If anything the permissibility of patenting induced pluripotent stem cells may encourage researchers to abandon the pursuit of human embryonic stem cells and endeavour to further explore induced pluripotent stem cells.

That said, a major issue which has delayed investment into induced pluripotent stem cell research is the fact that over broad patents are being issued to large companies, which has caused little leeway for smaller investors to recoup any money devoted to more detailed stem cell research.

Through the appraisal of the legal issues and questions pertaining to both embryonic and induced stem cells it does not appear as if the introduction of induced pluripotent stem cells as an alternative alleviates the majority of the legal issues of human embryonic stem cells.

Further research into harmonizing stem cell laws and regulations is recommended to take place worldwide, as well as clarification and solutions to legal questions which may affect stem cell research such as informed consent, over-broad patenting, and the legal interpretations of biological boundaries. The importance of human embryonic stem cells ought to be highlighted as well. To perfect the technique of inducing pluripotency, such stem cells will need to be compared to the 'Golden Standard' of embryonic stem cells. Until this standard has been reached, and all scientific barriers have been overcome, induced pluripotent stem cells will not be employed to their fullest extent.

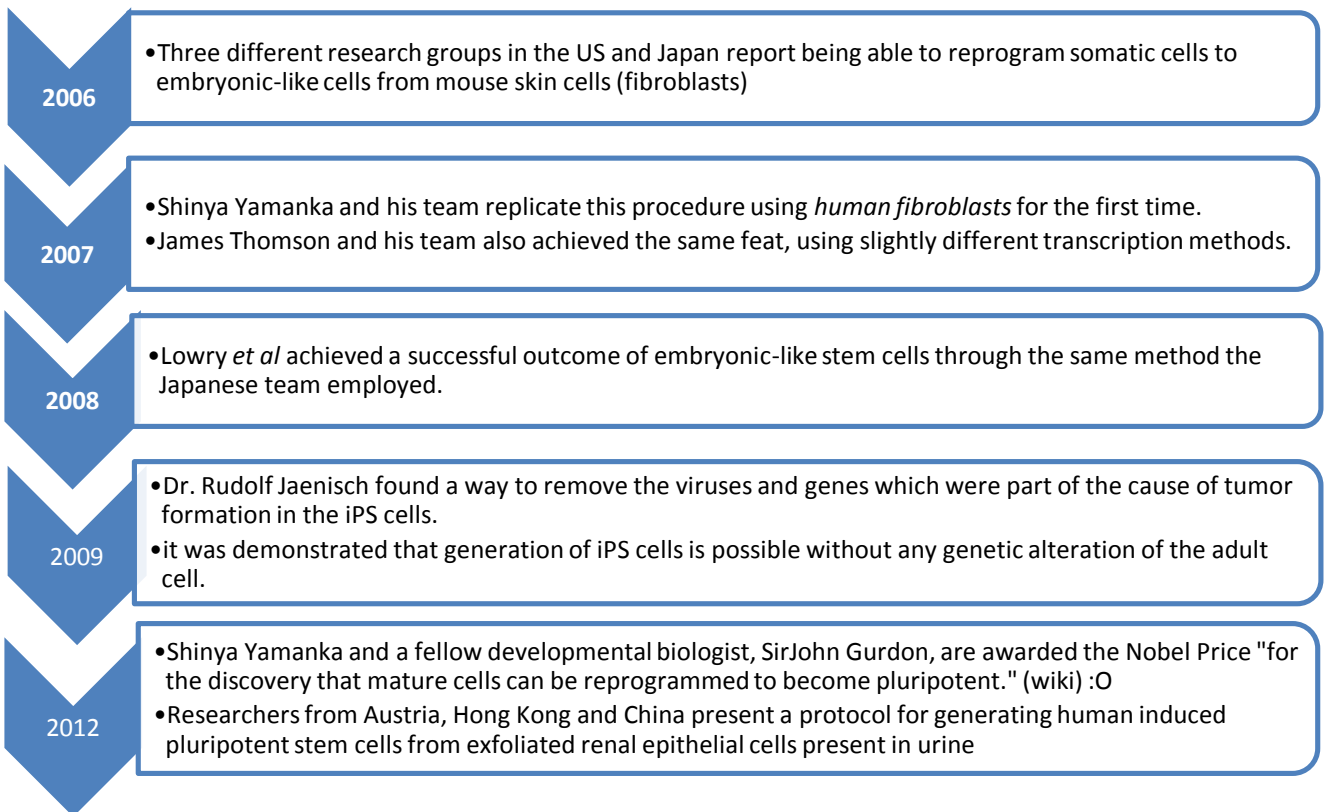
While the promise of a life devoid of disease is within our reach, significantly more research is needed to make such an ideal a reality.

While induced pluripotent stem cells resolve the majority of ethical issues related to human embryonic stem cells, they also generate ethical issues of their own. As well as this, induced pluripotent stem cells do little to dissipate the majority of the legal issues related to human embryonic stem cells.

Appendix 1: Timeline



Appendix 1: Timeline Continued



Appendix 2: Comparison of Stem Cell Laws (7)

Country	Position to human embryonic stem cell Research	Laws or Court Decisions relating to human embryonic stem cell research	Advising Bodies
Ireland	-In 2008 there was a move to ban research on human embryos and to implement criminal charges if research took place, but this was never passed into law	- Withdrawn: Stem Cell Research (Protection of Human Embryos) Bill 2008 - Lapsed: Human Body Organs and Human Tissue Bill 2008 -M.R. vs. T.R.	- Abolished: Irish Council of Bioethics -Irish Medical Council
UK	-Allowed, subject to a licence from the HFEA -Embryos can be created <i>only</i> for research purposes -This licence only covers research on embryos created <i>in vitro</i> up to 14 days old	-Human Fertilisation and Embryology Act 1990 & 2008 -Human Fertilisation and Embryology Regulations 2001 -Human Tissue act 2004 -Human Reproductive Cloning Act 2002	-Human Tissue Authority -HFE Authority -UK Stem Cell Initiative
Italy	-Derivation of embryonic stem cells is banned, but <i>imported</i> embryonic stem cell lines may be used for research	-Law 40, Regulation of Medically Assisted Human Reproduction, February 2004 -Referendum on Law 40, 2005	-Italian National Ethics Committee

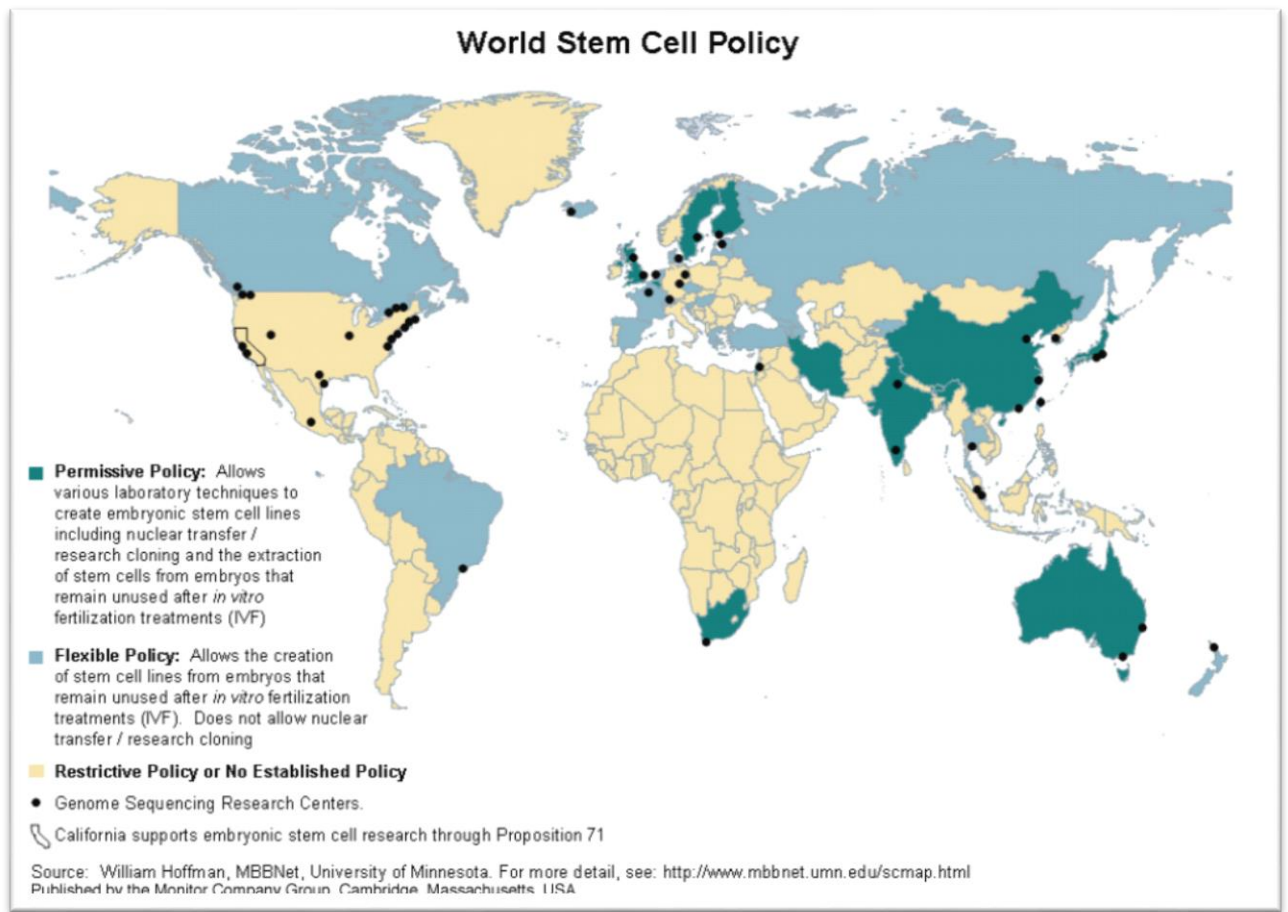
Appendix 2: Comparison of Stem Cell Laws Continued

Country	Position to human embryonic stem cell Research	Laws or Court Decisions relating to human embryonic stem cell research	Advising Bodies
Spain	<ul style="list-style-type: none"> -Research on embryos for therapeutic and research purposes is authorised -The creation of embryos specifically for research is allowed 	<ul style="list-style-type: none"> -Law on Biomedical Research (Law 14/2007) -Law on Assisted Reproductive Technology (Law 22/2006) -Law on Assisted Reproductive Techniques (Law 45/2003) 	<ul style="list-style-type: none"> -Guarantees Commission for the Donation and Use of Human Cells and Tissues -National Commission on Assisted Human Reproduction
France	<ul style="list-style-type: none"> -Research not allowed, except under specific conditions -Creation of embryos for research is banned 	<ul style="list-style-type: none"> -Law on Bioethics, LOI No 2011-814 2011 -Law on Bioethics, Law n. 2004-800 2004 -Law on Human Life, Law n. 94-653 1994 	<ul style="list-style-type: none"> -French Biomedicine Agency -French National Consultative Committee of Ethics
Germany	<ul style="list-style-type: none"> -Derivation of human embryonic stem cell is banned -Embryonic stem cell lines created before 1st May 2007 (originally 1st January 2002) can be imported for research purposes 	<ul style="list-style-type: none"> -Embryo Protection Act (Embryonenschutzes) 1991 -Stem Cell Act (Stammzellgesetz) 2002 -Act for the Protection of embryos 1990 -German Constitution, basic law, 1949 	<ul style="list-style-type: none"> -Central Ethics Commission for Stem Cell Research (ZES) -Germany National Ethics Council

Appendix 2: Comparison of Stem Cell Laws Continued

Country	Position to human embryonic stem cell Research	Laws or Court Decisions relating to human embryonic stem cell research	Advising Bodies
United States	<ul style="list-style-type: none"> -The creation of embryos specifically for research purposes is prohibited -Only research on already existing stem cell lines created prior to 9th August 2001 is permitted 	<ul style="list-style-type: none"> -Dickey-Wicker Amendment 1995 -Stem Cell Therapeutic and Research Act 2005 -Roe v. Wade 1973 -Individual State laws range from outright banning human embryonic stem cell research to funding its development 	<ul style="list-style-type: none"> -NIH Human Embryo Research Panel -United States National Academies -Human Embryonic Stem Cell Research Advisory Committee -Centre for Biologics Evaluation and Research (CBER)
Japan	<ul style="list-style-type: none"> -Research is allowed for therapeutic purposes 	<ul style="list-style-type: none"> - Pharmaceutical Affairs Law 	<ul style="list-style-type: none"> -Ministry of Health, Labour and Welfare (MHLW) -Pharmaceuticals and Medical Device Agency (PMDA)
European Union & The Council of Europe	<p>Due to the diversity of philosophical, social, cultural and religious influences of each member state, the EU has not issued a direct law in relation to human embryonic stem cell research.</p>	<ul style="list-style-type: none"> -EU Tissues and Cell Directive 2004/23/EC -European Convention on Human Rights and Biomedicine (1997) 	<ul style="list-style-type: none"> -Group of Advisors on the Ethical Implications of Biotechnology (now known as the EGE)

Appendix 3: World Map of Stem Cell Policies (57)



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