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PATENT FRAMEWORK FOR THE HUMAN STEM CELLS IN EUROPE AND THE USA: INNOVATION, ETHICS AND ACCESS TO THERAPY

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For

Begum Shamsunnahar

I dedicate my PhD to my best friend's mother Begum Shamsunnahar who lived young and died young.

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ARIF JAMIL
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	ABBREVIATION/ACRONYM
ACA	Affordable Care Act
ACT	Advanced Cell Technology[1]
ADMSC	Adipose Derived Mesenchymal Stem Cell
AEMPS	Agencia Española de Medicamentos y Productos Sanitarios (Spanish Agency of Medicines and Medical Devices)
AIA	America Invents Act
AIPA	American Inventors Protection Act
AMD	Age-related Macular Degeneration
APA	American Psychological Association
ARRA	American Recovery and Reinvestment Act
ASC	Adipose-derived Stem Cells
ADR	Adverse Drug Reaction
BIHR	British Institute of Human Rights
BNS	Baltic News Service
CFR	Code of Federal Regulations
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CiRA	Center for iPS Cell Research and Application
CIRM	California Institute for Regenerative Medicine
CoE	Council of Europe
CQC	Care Quality Commission
CJEU	Court of Justice of the European Union
CKT	Common Key Themes
CKW	Common Key Words
CLI	Critical Limb Ischemia
DER	Data Exclusivity Right
DNA	Deoxyribonucleic Acid
EBoA	Enlarged Board of Appeal
ECHR	European Convention on Human Rights
ECJ	European Court of Justice
ECtHR	European Court of Human Rights
EEA	European Economic Area
EGE	European Group on Ethics in Science and New Technologies
EHIC	European Health Insurance Card
EMA	European Medicines Agency
EN	Endoderm
EP	European Patent
EPC	European Patent Convention
EPO	European Patent Office
ES	Embryonic Stem
ESC	Embryonic Stem Cell
EU	European Union

[1] On November 14, 2014, Advanced Cell Technology (ACT) changed its corporate name to "Ocata Therapeutics, Inc.".

Evo-Devo	Evolutionary Developmental Biology
FDA	Food and Drug Administration
FOXH1	Forkhead box H1
FPG	Federal Poverty Guideline
GA	Gestational Age
GAEIB	Group of Advisors on the Ethical Implications of Biotechnology
GNI	Gross National Income
GU	Gazetta Ufficiale
hBMC	Human Bone Marrow Cells
HDF	Human Dermal Fibroblasts
hESC	Human Embryonic Stem Cell
HFEA	Human Fertilisation and Embryology Authority
hiPSC	human induced Pluripotent Stem Cells
HLA	Human Leukocyte Antigen
hMSC	Human Mesenchymal Stem Cell
hPSC	Human Pluripotent Stem Cell
hPSCR	Human Pluripotent Stem Cell Research
hPSCI	Human Pluripotent Stem Cell based Invention
hpSC	Human Parthenogenetic Stem Cell
HRA	Health Research Authority
hSC	Human Stem Cell
hSCR	Human Stem Cell Research
hSCI	Human Stem Cell based Inventions/Innovations
HSP	Human Subject Protection
HTA	Health Technology Assessment
IACUC	Institutional Animal Care and Use Committee
IBMHO	Inventions/Innovations that use Biological Materials of Human Origin
ICCPR	International Covenant on Civil and Political Rights
ICESCR	International Covenant on Economic, Social, and Cultural Rights
ICM	Inner Cell Mass
IDC	Indirect Cost
IHC	Individual Health Coverage
IP	Intellectual Property
IPAB	Intellectual Property Appellate Board
IPR	Intellectual Property Right
iPSC	Induced Pluripotent Stem Cells
IRB	Institutional Review Board
IRS	Internal Revenue Service
ISCO	International Stem Cell Corporation
ISSCR	International Society for Stem Cell Research
IMP	Investigational Medicinal Product
IVF	In-Vitro Fertilization
JPO	Japan Patent Office
KLF4	Kruppel-Like Factor 4
LDC	Least Developed Country
LMP	Last Menstrual Period

MAH	Marketing Authorisation Holder
ME	Mesoderm
MRI	Magnetic Resonance Imaging
MSC	Mesenchymal Stem Cells
NBAC	National Bioethics Advisory Commission
NBC	National Bioethics Committee (Comitato nazionale per la bioetica)
NCI	National Cancer Institute
NE	Neuroectoderm
NEI	National Eye Institute
NHBE	Normal Human Bronchial Epithelial Cell
NHMRC	National Health and Medical Research Council
NHS	National Health Service
NHSL	National Health System of Lithuania
NIBSC	National Institute for Biological Standards and Control
NICE	National Institute for Health and Care Excellence
NIH	National Institute of Health
NLM	National Library of Medicine
NP	National Patent
NPO	National Patent Office
NT-ESC	Nuclear Transfer Embryonic Stem Cells
NT-hPSC	Nuclear Transfer Human Pluripotent Stem Cell
NYSCF	New York Stem Cell Foundation
OHSU	Oregon Health & Science University
OR	Odds Ratio
OSKM	OCT3/4, SOX2, KLF4 and c-MYC
PASSI	Progressi delle Aziende Sanitarie per la Salute in Italia[2]
PCT	Patent Cooperation Treaty
PNHP	Physicians for a National Health Program
pn-hPSC	Parthenote Derived Human Pluripotent Stem Cells
PrEC	Prostate Epithelial Cells
PIP	Poly Implant Prothese
PLT	Patent Law Treaty
PPACA	Patient Protection and Affordable Care Act
PVP	Plant Variety Protection
QCA	Qualitative Content Analysis
RDE	Regulatory Data Exclusivity
R&D	Research and Development
REC	Research Ethics Committee
RNA	Ribonucleic Acid
RPE	Retinal Pigment Epithelium
SACK	Suppression of Asymmetric Cell Kinetics
SC	Stem Cell
SCNT	Somatic Cell Nuclear Transfer
SD	South Dakota

[2] Italian surveillance system for the progress in medical health.

SHI	Statutory Health Insurance
shRNA	Short Hairpin RNA
SMD	Stargardt Macular Dystrophy
SNU	Seoul National University
SSN	Servizio Sanitario Nazionale (National Health Service)
S&T	Science and Technology
TC	Tetraploid Complementation
TE	Trophectoderm
TEU	Treaty on European Union
TFEU	Treaty on the Functioning of the European Union
TRIPS	Agreement on Trade-Related Aspects of Intellectual Property Rights
TSI	Tarjata Sanitaria Individual[3]
TSM Test	Teaching-Suggestion-Motivation Test
UDHR	Universal Declaration of Human Rights
UKIPO	United Kingdom Intellectual Property Office
UKT	Unique Key Themes
UKW	Unique Key Words
UMC	Uppsala Monitoring Centre
UN	United Nations
UNESCO	United Nations Educational, Scientific and Cultural Organization
UP	Unitary Patent
UPC	Unified Patent Court
UPOV	International Union for the Protection of New Varieties of Plants
USPTO	U.S. Patent and Trademark Office
WARF	Wisconsin Alumni Research Foundation
WHO	World Health Organization
WIPO	World Intellectual Property Organization
WMA	World Medical Association
WTO	World Trade Organization

[3] Health card from the Department of Social Security, Spain.

Case List

CHAPTER 1

INTRODUCTION, PROBLEM SPACE, RESEARCH QUESTIONS, RESEARCH AIMS, METHODOLOGY AND OUTLINE OF THE THESIS

1.1 INTRODUCTION

The monograph is a research work of interdisciplinary nature. It has special implications for the IP protection of human Stem Cell based Inventions/Innovations (hereinafter referred to as hSCI). Human Stem Cell Research (hereinafter referred to as hSCR) and patent/IP protection of hSCI have been examined from the legal, ethical and scientific perspectives. The laws and policies of Germany, Italy, Lithuania, Spain and the United Kingdom in Europe and California, Massachusetts, New Jersey, South Dakota and Texas from amongst the States in the USA are revisited for the writing of the monograph. The "hSCR policy" and "provisions on exclusion from patent" are different in different jurisdictions. Stem cell research policies are different (from restrictive to liberal) among Germany, Italy, Lithuania, Spain and United Kingdom. Significant differences can be observed in hSCR policy within the USA. Although the Federal policy is liberal, there are differences in the State level. Liberal policy can be observed in the California, Massachusetts and New Jersey but restrictive/conservative policies are prevalent in Texas and South Dakota. The *reason for selection of those countries* is that they follow "different stem cell research policies" and also have "different provisions on exclusion from patentable inventions."

This work comes after several groundbreaking events have taken place in the related fields. To name few:

- The Unitary Patent Package is taking off in Europe;
- In *National Federation of Independent Business, et al. v. Sebelius, Secretary of Health and Human Services, et al*. (2012),[1] the Affordable Care Act 2010 survived in most part in the United States Supreme Court;
- Two very relevant cases on the subject were decided differently in two continents, i.e., *Brüstle* (2011)[2] and *Sherley* (2012);[3]
- Three years after the case of *Oliver Brüstle v.Greenpeace e.V.* (2011),[4] the CJEU took more liberal approach towards the human stem cell patents in the case of *International Stem Cell Corporation v. Comptroller General of Patents, Designs and Trade Marks*(2014);[5]
- The first iPSC human trial in Japan took place, etc.

Therefore, an interdisciplinary study examining "the techniques of hSCR, ethical and legal intricacies involved and the patent protection of hSCI" is a very timely exercise.

The thesis aims to explore "the adequacy of the patent system for the hSCI at present", along with the ethical and bioethical issues involved in the context. Therefore, it attempts to answer what is the

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[1] 567 U.S. ___ (2012), 132 S.Ct 2566.

[2] Oliver Brüstle v. Greenpeace e. V., C-34/10, Judgment of the Court (Grand Chamber) 18 Oct. 2011, also *available at* http://curia.europa.eu/juris/liste.jsf?language=en&num=C-34/10 (last visited July 25, 2014).

[3] No. 11-5241, Slip op. at 8 (D.C. Cir. August 24, 2012).

[4] *Brüstle*, *supra* note 2.

[5] Case C‑364/13, 18 Dec. 2014, also *available at* http://curia.europa.eu/juris/document/document.jsf;jsessionid=9ea7d0f130de9c4121923b8f43769c42c1706a04f989.e34KaxiLc3eQc40LaxqMbN4ObheSe0?text=&docid=160936&pageIndex=0&doclang=EN&mode=lst&dir=&occ=first&part=1&cid=88991#Footnote*(last visited Dec. 22, 2014).

best possible way to offer intellectual property right (IPR) to those inventions/innovations that would create environment for wider accessibility to the therapy in one hand and allow adequate incentive for innovation on the other hand. In order to find answer to the above queries an empirical research was also carried out. The primary investigation was conducted through a *partly completely-structured, partly open-ended online (email) questionnaire* in which experts on bioethics, life science and intellectual property law were interrogated. The study took place between 6th September 2013 and 29th January 2014. A total number of 31 respondents participated in the primary investigation.[6]

1.2 IDENTIFYING THE MAJOR PROBLEMS

Human Stem Cell Research (hSCR) is an area where significant differences exist (regarding the purview of research and the patent protection) among the countries due to prevailing political, economic, social and cultural conditions. Despite Europe's recent Unitary Patent package, the fast growth of biomedical research and inventions/innovations from evolutionary developmental biology (Evo-Devo) is becoming hard for the patent law to cope up with. The widening of the purview of patent law for inventions/innovations in those fields of science that uses human biological material obscures the boundary of the patentability criteria. Countries perceive the spirit of bioethics differently for the hSCR. So far, the patent had been the mostly exercised IP protection tool for the inventions from the biomedical research and Evo-Devo using human biological material. One important kind of hSCR is the human embryonic stem cell (hESC) research. Inventions encompassing the destruction of human embryo have been excluded from patent protection in Europe by the decision of the Court of Justice of the European Union (hereinafter referred to as CJEU) in *Brüstle's* case.[7] On the contrary, the funding of the National Institute of Health (NIH) is again made available in the US after the U.S. Court of Appeal for the District of Columbia concluded in favor of removal of the injunction on funding for stem cell research in the case of *Sherley v. Sebelius*.[8] Patent is available in the US for hESC based inventions that employ supernumerary embryos, i.e., the embryos that are no longer required for the fertility purpose, in other words, the IVF redundant embryos. Germany, Italy, Lithuania, Spain and United Kingdom- all have different stem cell research policies (ranging from restrictive to liberal).

Safety of human subject and patient is a major concern for all emerging stem cell based inventions/innovations. Ethical issues being understood from different perspectives, can be invoked in almost all of the stem cell researches. At present, there is not much uniformity in the ideology and practice of patent protection in the field of hSCI. Uncertainty of patent protection and patenting hSCI both have many repercussions. The irreconcilable differences about ethical interpretation regarding the legitimacy of stem cell research and means of protection of the inventions among countries is the driving force for my research to explore a functional recommendation. The recommendations/proposals I am making after the analysis of the empirical study, is expected to maintain a balance among the three important aspects, i.e.,

- offering *incentive to invention/innovation*,
- allowing the *access to therapies* at an affordable expenses and
- *mitigating the ethical debate* to a significant extent.

The existing patent system is multilayered in Europe. Extremely strong IP protection of inventions that are meant for health care may have been detrimental to "access to therapy." Without proper IP

[6] The respondents are coming from 16 countries representing most of the continents, i.e., Africa, Americas, Asia and Europe.
[7] *Brüstle*, *supra* note 2.
[8] No. 11-5241, Slip op. (D.C. Cir. August 24, 2012).

protection there may be dearth in research and innovation. A balanced approach is missing in the current patent system that protects inventions having implications for health care. Moreover, fast changes and breakthrough developments in the protocol of hSCR call for the revisiting of the IP protection framework and ethical boundaries, thereby, posing legal challenges.

1.3 THE RESEARCH QUESTIONS OF THE MONOGRAPH

The *research questions* of the monograph are the following:

I. What is the best way to offer IP protection to "human Stem Cell based Inventions/Innovations" (hSCI) / "Inventions/Innovations that use Biological Materials of Human Origin" (IBMHO) that would ensure incentive for invention/innovation and allow wider access to therapies?
II. What are the legal/ethical/bioethical issues in human Stem cell Research (hSCR) and what needs to be addressed for "ethical" hSCR?
III. What does an empirical investigation and a qualitative analysis reveal from a survey conducted amongst the experts in order to answer the research question nos. I and II?

1.4 RESEARCH AIMS AND OBJECTIVES

The objectives are:

I. To explore the ethical[9] issues involved in the hSCR;

II. To revisit "the legal framework of hSCR" and "IP protection regime built by patent for the hSCI", while observing the prevailing circumstances and divergence in the select country context;

III. To find how the experts as respondents view the "ethical and legal issues in hSCR" and "patent/IP protection of hSCI" through an empirical investigation;

IV. To make limited recommendations on modernizing intellectual property protection for the hSCI/IBMHO; and

V. To make recommendations for addressing the ethical issues and for fostering access to the therapy.

The aim is to achieve and find a balance among the three main aspects, i.e., innovation, ethics and access to therapy. In order to achieve those aims and objectives, both theoretical and empirical investigations were conducted.

[9] "Ethics" is a general term reflective of the societal/collective perception towards an action. "Morality" is the individualistic embodiment of a virtue; differs between individuals.
The terms "ethics" and "morality" have not been redefined in this monograph. They shall be deemed to have retained their conventional and literal "meaning and differences".

1.5 METHODOLOGY

The Monograph is comprised of both theoretical and empirical parts.

The monograph encompasses the following topics and exercises:

- Stem cell research;
- Examination of ethics and bioethics;
- Health care policy;
- Access to therapy;
- Patent framework;
- Qualitative Content Analysis of the Survey data.

1.5.1 THE THEORETICAL DISCUSSION

The laws and policies on human stem cell research and patent protection of Germany, Italy, Lithuania, Spain and the United Kingdom in Europe and California, Massachusetts, New Jersey, South Dakota and Texas from amongst the States in the USA are revisited for the theoretical discussion of the monograph.

For the theoritical discusion, the scientific developments already taken place in the field of human stem cell research were examined and the ethical issues involved in those select techniques were detailed. The legal frameworks of stem cell research and the patent protection in those countries were revisited by way of a comparative study. Among other issues, the comparative discussion highlighted the legal, ethical and bioethical issues in hSCR, access to the therapy and IP/patent protection of hSCI.

The relevant cases, international conventions, treaties, community legislation in Europe and the Federal laws in the USA in the study context are painstakingly examined. Patent database and clinical trial database were well-investigated. Patents (US patents/EP) granted/filed for the recent and select human stem cell based inventions were examined.

1.5.2 THE EMPIRICAL RESEARCH

The primary investigation (empirical research) began in the 1stweek of September 2013 by sending email to the experts and the questionnaire in attachment as Microsoft word document. This process of sending questionnaire and receiving answers continued until last week of January 2014. Therefore, the survey can be said to be conducted in a time frame between September 2013 and January 2014. The *convenience sampling* approach was adopted for collection of the responses. The answers received were voluntary submission of the respondents to my inbox of the email account aaajamil@yahoo.com.

As the experts/respondents participating in the study come from several different continents, email correspondence was the most effective means of communication. The emails are preserved and in some cases, the respondents have clarified the queries, if there were any ambiguity.

The respondents were free to choose from the suggested options in the questionnaire, change and alter the suggested answers, write a new answer or make any comment. The design of the questionnaire *allowed the respondents to be creative and ensured their best self-representation*. Therefore, a semi-structured/mixed-type questionnaire was the appropriate instrument for this study and the Qualitative analysis was conducted on the comments made by the respondents.

1.5.2.1 METHODOLOGY OF THE EMPIRICAL RESEARCH

The primary investigation was conducted through a partly completely-structured, partly open-ended questionnaire in which experts on bioethics, life science and intellectual property law were inquired to give their responses.

Key information about the study is as follows:

i. Total participant 31; Total country 16.[10]
ii. Participating respondents are from diverse backgrounds.
iii. Highest number of the respondents belonging to a single country is Lithuania. Several respondents are from Italy and the USA. Two respondents are from Egypt and rest of the respondents individually represents his/her country.

Table 1.1 Country of the Respondents

Country	**Frequency**	**Percent**	**Cumulative %**
Bangladesh	1	3.23	3.23
Botswana	1	3.23	6.45
Chile	1	3.23	9.68
India	1	3.23	12.9
Denmark	1	3.23	16.13
Egypt	2	6.45	22.58
Kyrgyzstan	1	3.23	25.81
Malaysia	1	3.23	29.03
Italy	5	16.13	45.16
Japan	1	3.23	48.39
Lithuania	8	25.81	74.19
Spain	1	3.23	77.42
Suriname	1	3.23	80.65
UAE	1	3.23	83.87
USA	4	12.9	96.77
Mexico	1	3.23	100
Total	**31**	**100**	

[10] The continents are Africa, America, Asia and Europe.

1.5.2.2 THE RESPONDENTS AT A GLANCE

The diverse professional backgrounds of the participating respondents and the country they represent are summarized in table 1.2 and 1.1, respectively.

Table 1.2 Profession of the Respondents

Profession	**Frequency**	**Percent**	**Cumulative %**
Academic (any field)	2	6.45	6.45
Ethicist/Bioethicist	2	6.45	12.9
Lawyer	5	16.13	29.03
Patent Examiner	2	6.45	35.48
Patient Advocate	2	6.45	41.94
Physician	1	3.23	45.16
Researcher (any field)	2	6.45	51.61
Academic & Lawyer	3	9.68	61.29
Academic & Researcher	3	9.68	70.97
Academic, Bioethicist & Physician	1	3.23	74.19
Academic, Bioethicist & Lawyer	1	3.23	77.42
Academic, Lawyer & Patient	1	3.23	80.65
Bioethicist & Lawyer	1	3.23	83.87
Bioethicist & Researcher	1	3.23	87.1
Lawyer & Scientist	1	3.23	90.32
Patent Examiner & Researcher	1	3.23	93.55
Scientist & Researcher (any field)	2	6.45	100
Total	**31**	**100**	

1.5.2.3 PURPOSE AND GOALS OF THE EMPIRICAL RESEARCH

As the questionnaire was exploring the adequacy of the patent system and ethical issues in hSCR, the findings from the data analysis of the empirical investigation are likely to strengthen the conclusions the monograph. Hence, the goal is to increase the credibility and weight of the monograph.

1.5.2.4 QUALITATIVE DATA ANALYSIS

Qualitative Content Analysis (QCA) was conduceted on the comments/opinion of the respondents. The QCA is restricted to the independent comments made by the respondents. Since some of the

respondents made "comments/other opinions", the qualitative data analysis performed here reflects the views and perceptions of those individuals.

1.5.2.4.1. DIVERSITY OF QUALITATIVE DATA ANALYSIS APPROACHES: APPLYING CONCEPTS OF THE CONVENTIONAL CONTENT ANALYSIS

In the realm of qualitative data analysis, there is a great diversity of approaches used for analyzing text data. Methodologies like ethnography, grounded theory, phenomenology, historical research, qualitative content analysis, etc. have been extensively used in a broad range of studies. However, the choice of analysis techniques and designs are guided mainly by the research questions in mind, type of data available and the amount of data transformation required to answer these questions. Accordingly, Qualitative Content Analysis (QCA) was deemed to be the most suitable method for analyzing the qualitative data derived from the present study. Hsieh and Shanon in their article defined QCA "as a research method for the subjective interpretation of the content of text data through the systematic classification process of coding and identifying themes or patterns" (2005, 1278). Among the three basic approaches to QCA, qualitative data analysis in this study reflects the conventional approach. In the conventional approach, researchers do not depend on existing theories for coding or categorizing the data. Rather coding and subsequent "themes" emerge from the data itself. New insights emerge from each respondent's unique perspectives. The study findings may be subsequently interpreted and compared with relevant published findings and prevalent theories. They can potentially contribute to expanding the existing body of knowledge and suggest future research (Hsieh and Shanon 2005,1279).

According to Richards and Morse (2007, 160):"A theme runs right through data and is not necessarily confined to a specific segment of text. However, once a theme is identified, you are more likely to see segments of text that are pertinent to it." The goal for formulating themes is, therefore, to identify the underlying subtleties of each response and this process requires considerable amount of data transformation. The extent of data transformation is dependent upon the amount and quality of data available. This study is based on a *semi-structured* or *mixed type questionnaire* and the amount of data available for qualitative analysis is rather *limited*. This is because in the open options the respondents were free to give "comment/other opinion" and only those individuals who gave such voluntary responses were included in the qualitative content analysis. Therefore, those who chose from the structured suggested options only, were not included in the qualitative analysis. An opinion of Dr. Mary Ellen Young[11]was sought on qualitative data analysis of the questionnaire and responses for this study. Based on her suggestion, the following methodology of conventional content analysis was performed (Figure 1.2). The extent of data transformation performed and the emergent key themes qualify this content analysis as a "Thematic survey" as depicted in Sandelowski and Barroso (Figure 1, Sandelowski and Barroso 2003, 908). The figure from Sandelowski and Barroso shows the continuum of data transformation where "No finding" and "Topical survey" findings on the left hand side represent data that are the least transformed and do not constitute research and qualitative research, respectively and "Interpretive explanation" on the farthest right represents the most evolved form of findings with the highest level of data transformation by the researchers (Sandelowski and Barroso 2003, 908).

[11] Clinical Professor, Department of Behavioral Science and Community Health, College of Public Health and Health Professions, University of Florida, Florida, USA.

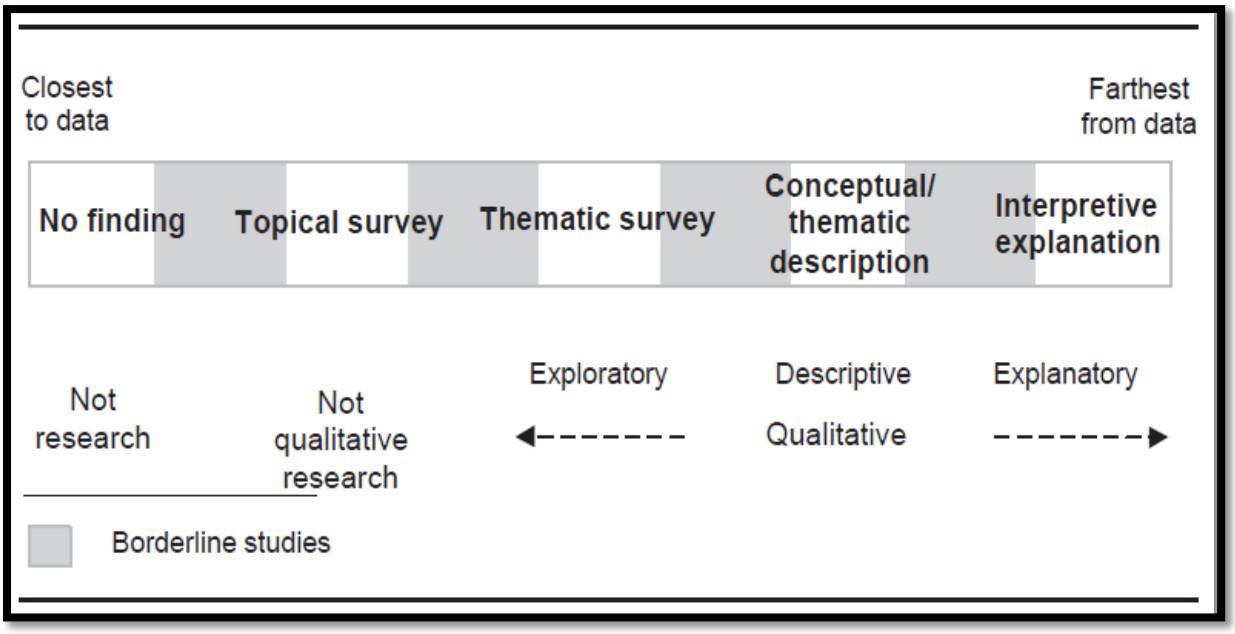

Fig. 1.1 "Typology of Qualitative Findings" (Figure 1, Sandelowski and Barroso 2003, 908)

Major steps comprising the QCA is depicted in figure 1.2. Details of the following methodology can be found in appendix V, VA and VB. Appendix VA and VB comprise of step one (1) performed separately by two different analysts.[12] Appendix V is the compilation of key words and major key themes (step 2-4) from both the analysts. Interpretation of the major key themes for each question and the overall summary is presented in chapters 5 and 6 of the monograph.

[12] Two analysts having different backgrounds are expected to have unique perspectives and yield a better quality of analysis. Analyst of appendix VA is Arif Jamil (Ph.D. Research Fellow (2012-2015) in Bioethics and Biolaw, Erasmus Mundus Joint International Doctoral Degree in Law, Science and Technology (LAST-JD); LL.M. in IP) and analyst of appendix VB is Tania S. Bonny (Ph.D. Research Fellow (2013 – Onward), Dept. of Environmental & Global Health, University of Florida, USA; Lecturer, Dept. of Microbiology, University of Dhaka, Bangladesh). Observations from both the analysts (developed in two separate appendices) were used to formulate "Common Key Themes (both analyst)" and "Unique Key Themes (one analyst)" which resulted in formulating the "Major Key Themes" and helped develop its interpretation.

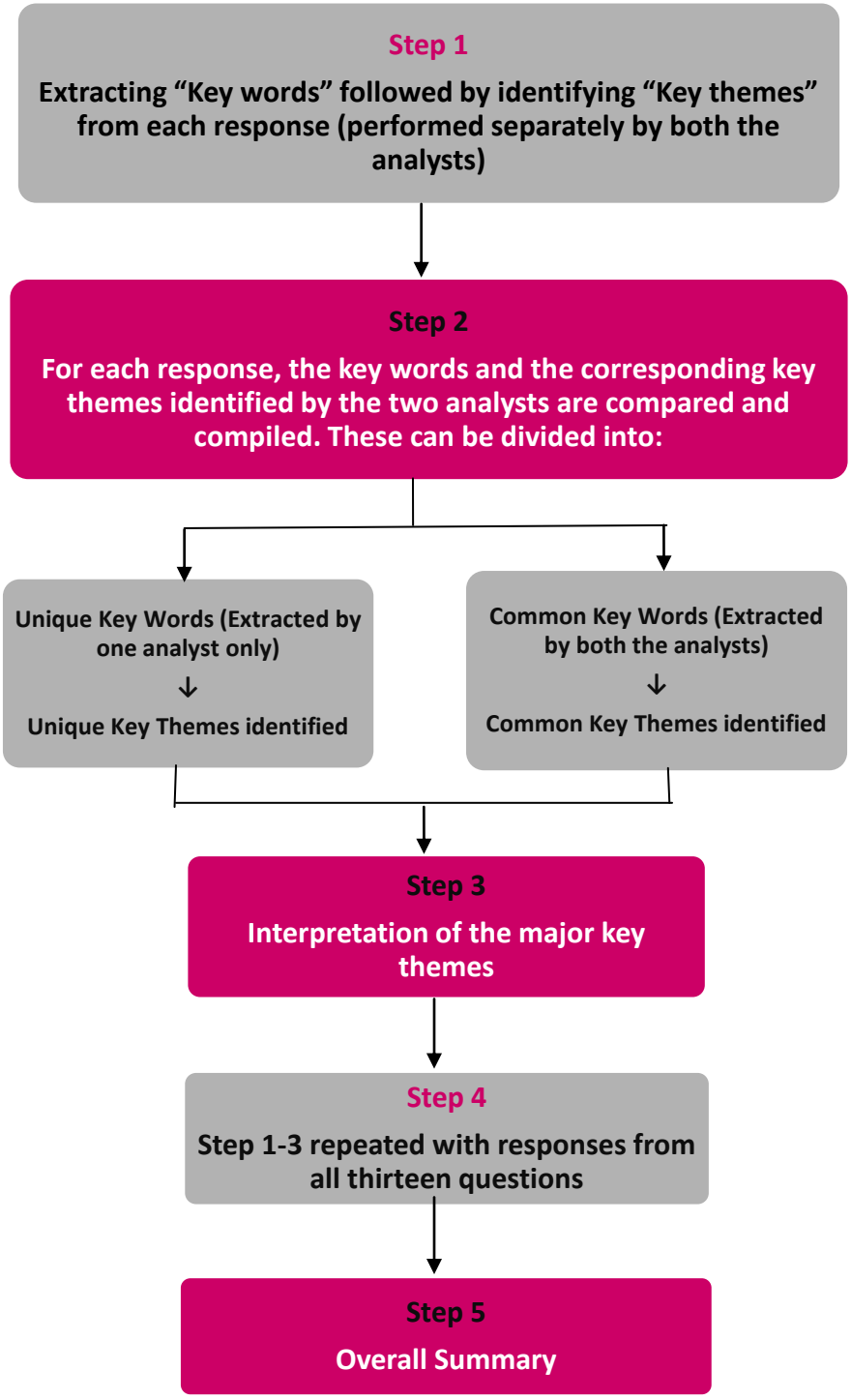

Fig. 1.2 Sequence of actions in the Qualitative Content Analysis (QCA)

1.6 OUTLINE OF THE THESIS

The Monograph consists of seven (7) chapters. They have hereinafter stated contents.

Ch. 1: INTRODUCTION:

This chapter deals with the problem space, research questions, research aims, methodology and outline of the thesis.

Ch. 2: DISCUSSION OF RELEVANT CONCEPTS:

Chapter 2 attempts to provide a *clarification of certain term/concept* in the research context. The definition of "human embryo", and an explanation of the expressions "human stem cell based invention/innovation" is provided.

Ch. 3: HUMAN STEM CELL RESEARCH AND INVENTION: ANALYSIS OF ETHICAL AND LEGAL ISSUES:

The most advanced techniques of derivation of human stem cells have been examined from the clinical and ethical perspectives in this chapter. They include:

- Human Embryonic Stem Cells (hESC) from the Inner Cell Mass (ICM) of the Blastocyst;
- Nuclear Transfer Embryonic Stem Cells (NT-ESC)/Somatic Cell Nuclear Transfer (SCNT);
- Induced Pluripotent Stem Cells (iPSC);
- Embryonic Stem Cells (ESC) from the blastomere cell of the pre-implantation stage embryo; and
- Human Parthenogenetic Stem Cells (hpSC).

Legal purview of hSCR, ethical and bioethical issues, access to the therapy, etc. were the important topics for the discussion in this chapter.

Ch. 4: ANALYSIS OF IPR ISSUES:

This chapter examined the patentability of hSCI and the "exclusions" from patenting. It talked about the divergence in the patent frameworks and the implications of divergence. Patent related concerns like regulatory data exclusivity, compulsory license, slim differences among the inventions, future legal complications, etc. were discussed in this chapter.

Ch. 5: QUALITATIVE DATA ANALYSIS:

This chapter is dedicated to qualitative data analysis (Qualitative Content Analysis (QCA)). Interpretation of the major key themes derived from the responses to all 13 questions is provided in this chapter.

Ch. 6: SUMMARY:

This chapter presents the summary of ethical and legal analysis and the summary on IPR issues.
The contents of the overall summary of the QCA can be found in this chapter.

Ch. 7: CONCLUSION AND FURTHER RESEARCH:

This chapter briefly presents the conclusions and future research.

The integral explanatory parts are the following appendices:

- Appendix I: Legal Framework;
- Appendix II: Questionnaire;
- Appendix III: Respondents;
- Appendix IV: Questions' Designs;
- Appendix V: Qualitative Analysis (Qualitative Content Analysis (QCA))
- Appendix VA: Analyst AJ;
- Appendix VB: Analyst Tania.

The additional contents are:

- Abbreviations;
- Acknowledgment;
- Case List; and
- Index.

CHAPTER 2

DISCUSSION OF RELEVANT CONCEPTS

2.1 CLARIFICATION OF THE KEY CONCEPTS IN THE RESEARCH CONTEXT

This chapter attempts to provide a definition of "human embryo", and an explanation for the expressions "human stem cell based invention/innovation".

Many of the techniques of derivation of human stem cells examined from the clinical and ethical perspectives in this thesis use embryo and cloned embryo. Those techniques are:

- hESCs from the ICM of the Blastocyst;
- ESC from the blastomere cell of the pre-implantation stage embryo; and
- NT-ESC/SCNT.

Certain use and destruction of the human embryo causes most of the ethical controversies in "hSCR and patenting of the hSCI," thereby, requiring sharp explanation of the term.

hSCR can result in both invention and innovation. Therefore, why the acronym hSCI shall mean the expressions "Human Stem Cell based Invention/Innovation" is explained here.

There could be clarification of many other scientific terms in this chapter, but throughout the monograph, footnotes clarified the concepts as and when deemed necessary. Some well-established concepts in the field of IP do not require any new explanation. An explanation on "human embryo" and "hSCI" was necessary to incorporate, as different authors may explain those concepts differently. Presenting them in a separate chapter allows to keep the other chapters less burdened.

2.1.1 HUMAN EMBRYO

What is human embryo? My intention here is to find a legal definition compatible to scientific explanations of the embryo. In fact, different legal texts use different connotations. What is deemed unacceptable from the ethical perspective would depend on how we have perceived the term "human embryo."

Clinical/Biological Definition of Human Embryo:

Clinical *gestational week* is calculated approximately 2 weeks earlier than the actual event of fertilization.[1] Embryonic period comprises of *Carnegie stages 1-23* which span through *week 1-8* following fertilization (UNSW Embryology: Human Development Timeline 2015; UNSW Embryology: Timeline human development 2015; Tania S. Bonny, in Dropbox with the researcher,

[1] William A. Engle ("*Lead author*") explained "Gestational age (completed weeks)" as "time elapsed between the first day of the last menstrual period and the day of delivery. If pregnancy was achieved using assisted reproductive technology, gestational age is calculated by adding 2 weeks to the conceptional age." (2004, 1363; italics in original).

It is not possible to determine the exact time/moment of the "fertilization event" in case of natural pregnancy, but it is possible in case of IVF. The procedures they use to inseminate eggs allow recording the time of fertilization. They just add 2 weeks more to this date to estimate expected delivery date. But in both cases, a 2-week Gestational Age (GA) is considered to calculate estimated delivery time.

For natural pregnancy: If doctors know the 1st day of LMP (Last Menstrual Period), they can estimate the approximate fertilization time, but not exactly. GA start from the first day of period ("first day of the last menstrual period" (Engle 2004, 1363)). From this date (first day of period) the unknown time of fertilization is approximately within 2 weeks (following ovulation, the time of effective conception is actually quite narrow).

For IVF: Fertilization time can be recorded. Then the embryo is implanted ("Transfer of the embryos" (The Johns Hopkins Fertility Center: In Vitro Fertilization (IVF) 2015)). GA is calculated by adding two more weeks to fertilization date. Then they estimate the probable delivery date.

April 18, 2015). So, *clinically* embryonic period ends at the *10th week of gestation* (UNSW Embryology: Human Development Timeline 2015; UNSW Embryology: Timeline human development 2015; Tania S. Bonny, in Dropbox with the researcher, April 18, 2015). Fetal period begins from *Carnegie stage 24 at week 9* (clinical gestational week 11) (UNSW Embryology: Human Development Timeline 2015; UNSW Embryology: Timeline human development 2015; Tania S. Bonny, in Dropbox with the researcher, April 18, 2015).

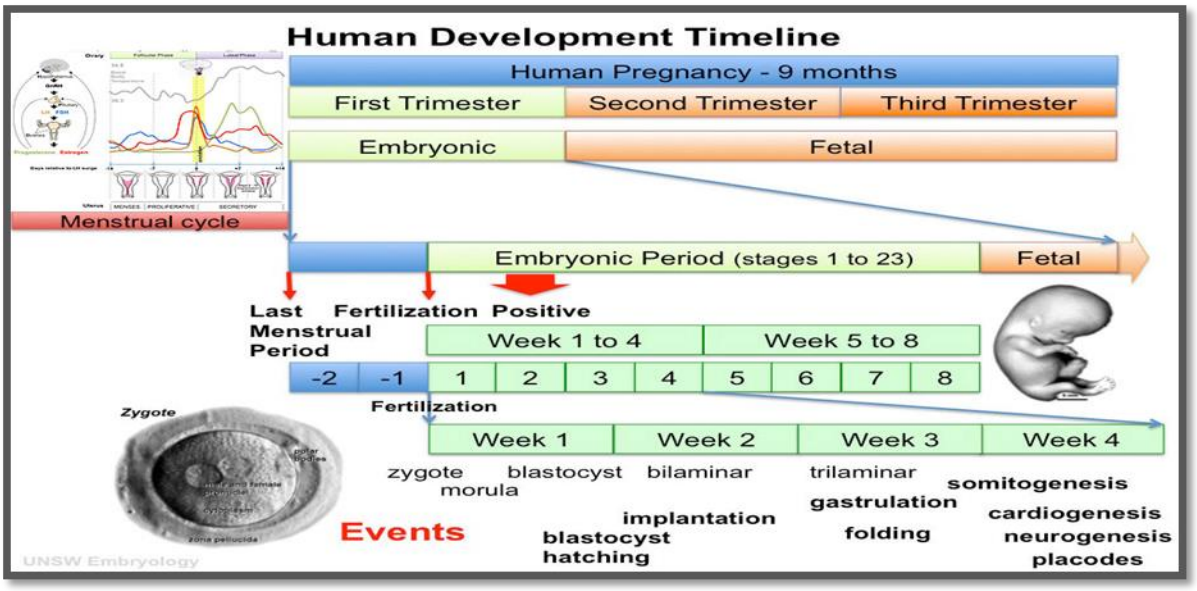

Fig. 2.1 "Human Development Timeline" (Illustration from UNSW Embryology: Human Development Timeline 2015)

The Discussion Paper of Australian Government National Health and Medical Research Council (NHMRC) drew the following (Figs. 2.2--2.9) "key events of the naturally occurring mammalian developmental processes" (Figure 1, Australian Government 2006, 7--8):

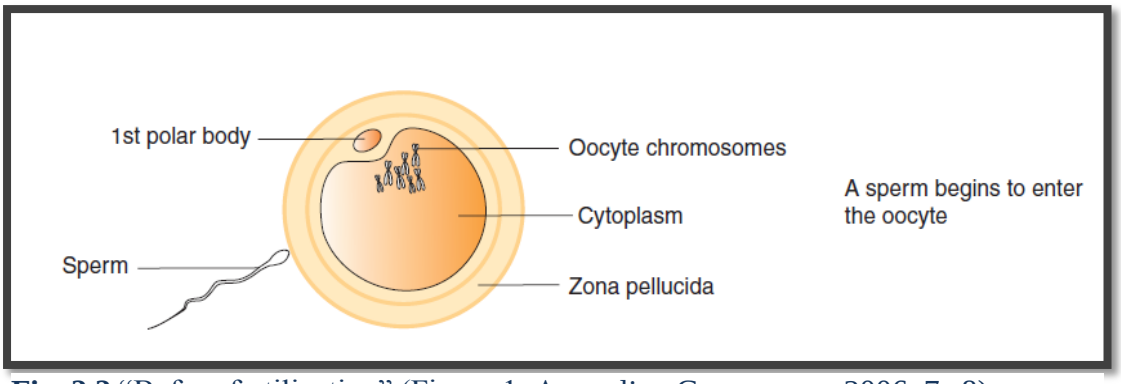

Fig. 2.2 "Before fertilization" (Figure 1, Australian Government 2006, 7--8)

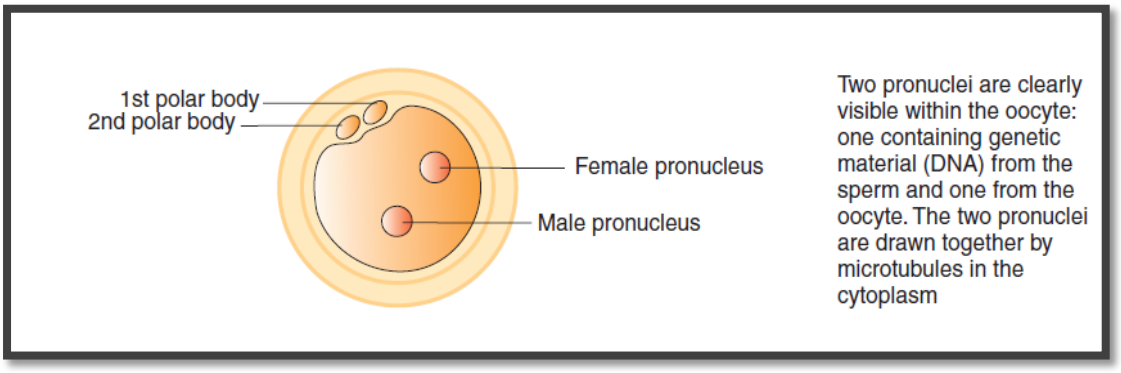

Fig. 2.3 "During fertilization" (Figure 1, Australian Government 2006, 7--8)

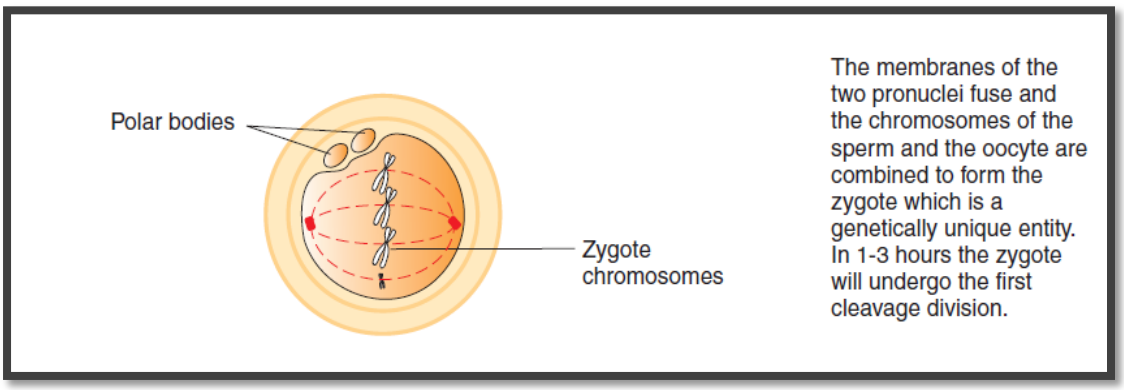

Fig. 2.4 "Fertilisation complete" (Figure 1, Australian Government 2006, 7--8)

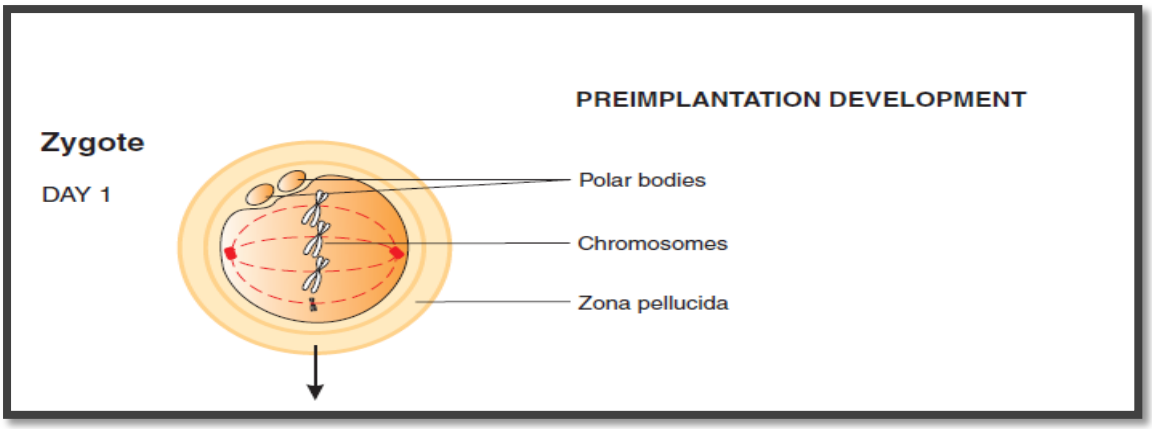

Fig. 2.5 "Zygote" (Figure 1, Australian Government 2006, 7--8)

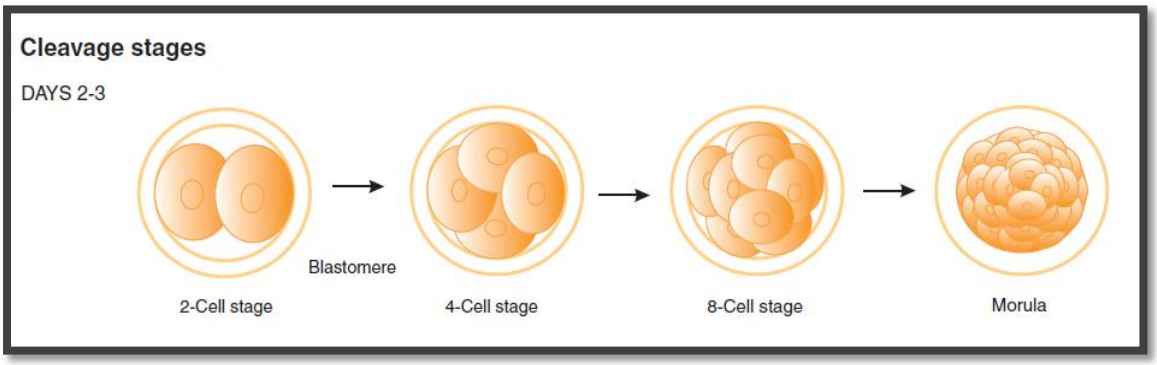

Fig. 2.6 "Cleavage stages" (Figure 1, Australian Government 2006, 7--8)

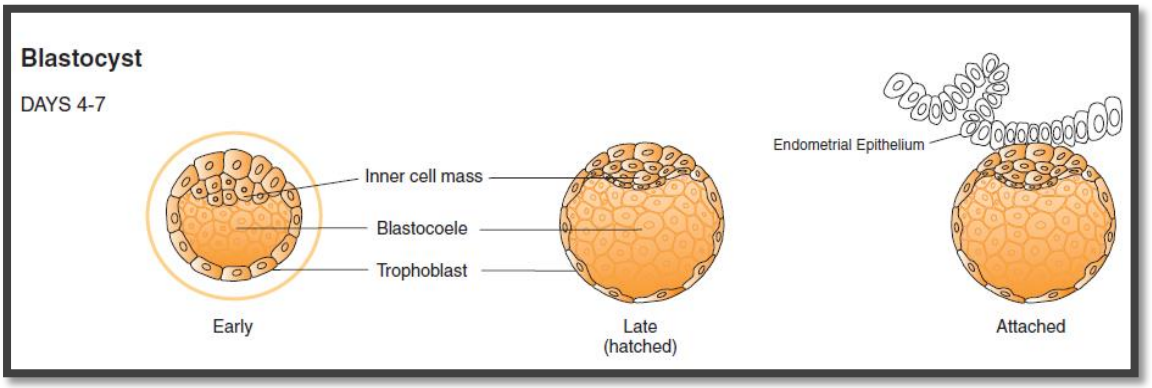

Fig. 2.7 "Blastocyst" (Figure 1, Australian Government 2006, 7--8)

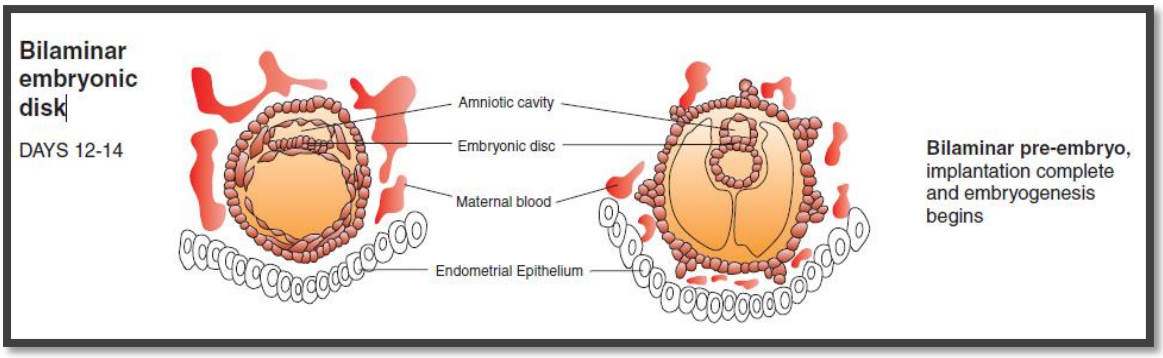

Fig. 2.8 "Bilaminar embryonic disk" (Figure 1, Australian Government 2006, 7--8)

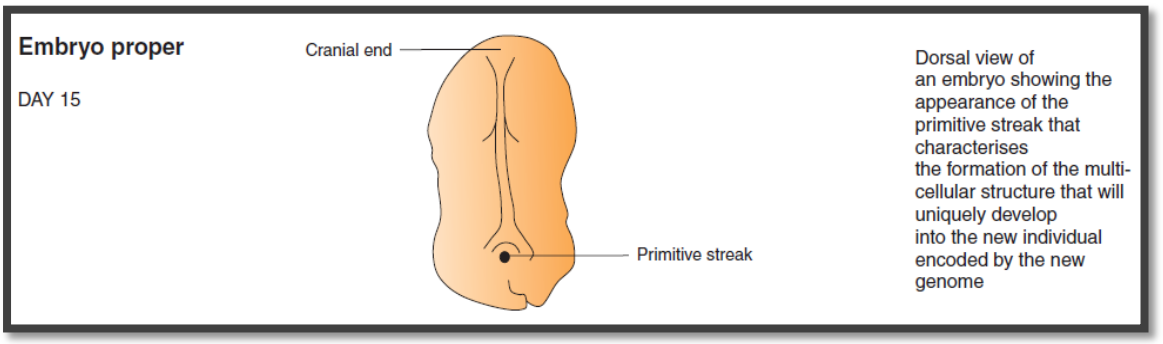

Fig. 2.9 "Embryo proper" (Figure 1, Australian Government 2006, 7--8)

When and at which stage (from what point following fertilization) we start calling the entity an "embryo"? Egle Radzeviciene,[2] a Lawyer and Scientist (Molecular Biology) said: "[The] term "embryo" lacks definition. It is unclear from which stage of development fertilized egg is deemed to be an embryo." (In email with the researcher, November 4, 2013).

Perception of Courts:

The judgment of *Brüstle* Case[3] has *defined* embryos or *identified* potential embryos even before the initiation of fertilization. Paragraph 53(1) of the Judgment of the Court (Grand Chamber) described the features and conditions that it considered as *embryo*: "any human ovum after fertilisation, any non-fertilised human ovum into which the cell nucleus from a mature human cell has been transplanted, and any non-fertilised human ovum whose division and further development have been stimulated by parthenogenesis constitute a 'human embryo'".[4] In the *International Stem Cell Corporation v. Comptroller General of Patents, Designs and Trade Marks* the CJEU held: "Article 6(2)(c) of Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions must be interpreted as meaning that an unfertilised human ovum whose division and further development have been stimulated by parthenogenesis does not constitute a 'human embryo', within the meaning of that provision, if, in the light of current scientific knowledge, it does not, in itself, have the inherent capacity of developing into a human

[2] Director, Intellectual Property, Thermo Fisher Scientific, Vilnius, Lithuania.
[3] Oliver Brüstle v. Greenpeace e.V., C-34/10, Judgment of the Court (Grand Chamber) 18 Oct. 2011, also *available at* http://curia.europa.eu/juris/liste.jsf?language=en&num=C-34/10 (last visited Aug. 07, 2014).
[4] *Id.*

being, this being a matter for the national court to determine."[5] Therefore, the combined reading of the *Brüstle* Case (2011) and *International Stem Cell Corporation* case (2014) leads to the conclusion that for the purpose of European patent, the parthenogenetically activated eggs will not be considered as human embryo if they lack the possibility/potential of developing into a human. The European Court of Human Rights in the case of *Costa and Pavan v. Italy*[6] used the term "embryo" for the organisms at the *pre implantation stage* of embryonic development.[7]

In *Litowitz v. Litowitz*,[8] the Washington Supreme Court in a dispute regarding the determination of fate of frozen or cryopreserved embryo originally created for fertility purpose referred the post fertilization cells/entity as "pre-embryo".[9] While referring the term pre-embryo, Smith J in that case[10] noted the following explanation by Donna A. Katz (about the term pre-embryo): "The term "preembryo" denotes that stage in human development immediately after fertilization occurs." (Katz 1998, 628n42).[11] Smith J also referred the explanation by Clifford Grobstein that says, it "comes into existence with the first cell division and lasts until the appearance of a single primitive streak, which is the first sign of organ differentiation. This [primitive streak] occurs at about fourteen days of development." (Katz, 1998, 628n42).[12]

In the Legal Texts of the Countries:

It seems that some of the Spanish legal texts use the term "pre-embryo" for the developing organism until the expiry of 14 days after the fertilization.[13] The "pre-embryos" are essentially those that are termed as "embryo" by the IVF clinics.[14] However, UK allows fertilized cells to develop *in vitro* until the expiry of 14 days.[15] Section 1(2)(1) of the Human Fertilisation and Embryology Act 2008 interprets and gives meaning of embryo as "embryo means a live human embryo" and it includes "an egg that is in the process of fertilisation or is undergoing any other process capable of resulting in an embryo."[16] So, the texts of Spain and UK refer the same/similar organism as "pre-embryo" and "embryo."

Embryo, according to Section 8(1) of the German Embryo Protection Act, "means the human egg cell, fertilised and capable of developing, from the time of fusion of the nuclei, and further, each

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[5] Case C - 364/13, Judgment of the Court (Grand Chamber) 18 Dec. 2014, paragraph 39, also *available at* http://curia.europa.eu/juris/document/document.jsf;jsessionid=9ea7d0f130de9c4121923b8f43769c42c1706a04f989.e34KaxiLc3eQc40LaxqMbN4ObheSe0?text=&docid=160936&pageIndex=0&doclang=EN&mode=lst&dir=&occ=first&part=1&cid=88991#Footnote* (last visited Dec. 22, 2014).

[6] Application no. 54270/10, European Court of Human Rights (Second Section) 28 Aug. 2012, also *available at* http://hudoc.echr.coe.int/sites/eng/pages/search.aspx?i=001-112993 (last visited April 14, 2015).

[7] They can be 2-5 days old.

[8] 48 P.3d 261 (Wash. 2002).

[9] *Id.*

[10] Litowitz v. Litowitz, *supra* note 8.

[11] *Id.*

[12] *Id.*

[13] Ley 14/2006, de 26 de mayo, sobre técnicas de reproducción humana asistida [Law 14/2006, of 26 May, on Assisted Human Reproduction Techniques] (B.O.E. 2006, 9292), art. 15 (Spain), *available at* http://www.boe.es/boe/dias/2006/05/27/pdfs/A19947-19956.pdf (last visited Feb. 13, 2015); Ley 14/2007, de 3 de julio, de Investigación biomedical [Law 14/2007, of 3 July, on Biomedical Research] (B.O.E. 2007, 12945), art. 32, 33 (Spain), *available at* http://www.boe.es/boe/dias/2007/07/04/pdfs/A28826-28848.pdf (last visited Feb. 24, 2015);

[14] Only difference is that the IVF clinics would be inclined to use them within 5/6 days of cell differentiation process after fertilization, for reproductive purposes.

[15] Human Fertilisation and Embryology Act, (1990) secs. 3(3)(a); 3(4) (U.K.), *available at* http://www.legislation.gov.uk/ukpga/1990/37/section/3 (last visited April 14, 2015).

[16] Human Fertilisation and Embryology Act, (2008) secs. 1(2)(1)(a); 1(2)(1)(b) (U.K.), *available at* http://www.legislation.gov.uk/ukpga/2008/22/section/3 (last visited April 14, 2015).

totipotent cell removed from an embryo that is assumed to be able to divide and to develop into an individual under the appropriate conditions for that." [17] This definition includes as embryo:

(a) human eggs from the moment of fertilization; and
(b) each *totipotent* cells derived from that developing/growing organism.

Cells remain *totipotent* until 4-8 cell stage of the embryonic development; this assessment varies in different cited sources. Then further cell division occurs and each cell no longer remains *totipotent*.

Lithuanian definition of human embryo specifies the length of the developmental phase; and it is human embryo until the end of 8th week from the formation of the zygote.[18] In the 9th week, Lithuanian law calls the organism "fetus," and until birth it is called so.[19] According to the Lithuanian definitions, there are two defining name of the human organism in the developmental phase, i.e., embryo and fetus. The "embryo" starts from the formation of the "zygote" and the "fetus" ends at birth.[20]

The embryo is defined in Section 2, Chapter 27 of the Acts of 2005 on "Enhancing Regenerative Medicine" for the State of Massachusetts, as "an organism of the species homo-sapiens whether formed by fertilization, somatic cell nuclear transfer, parthenogenesis or other means."[21] However, hESC research is allowed in that State.[22] According to the Codified Law on Public Health and Safety of South Dakota, "human embryo, means a living organism of the species Homo sapiens at the earliest stages of development (including the single-celled stage) that is not located in a woman's body."[23] It means zygote formed *in vitro* is an embryo for the purpose of this definition. In South Dakota, non-therapeutic research encompassing destruction of embryo is prohibited.[24]

Other Different Sources:

Is the single cell "zygote" (right after the fertilization) or after the implantation of the blastocyst, the growing organism would be called embryo? Advanced Fertility Center of Chicago, an IVF clinic, for all IVF purposes uses the term "embryo" for the 2 and 3 days old fertilized cells and to refer to 5 days' old blastocyst uses the term "embryo" as well (Advanced Fertility Center of Chicago 2013).

In the chronological stages of the embryonic development, different terminologies are used to indicate different stages of the developing embryo, e.g., morula, blastula, blastocyst, gastrula. In medical science, all the developing components has been clearly identified and we have merged and divided them as and when necessary for the interpretational purposes. The brain formation commences in 3-5th week of development (The Danish Council of Ethics 2004, 19) or 5th week of gestational age (NIH MedlinePlus Fetal Development 2013). More studies are needed to know the

[17] Gesetz zum Schutz von Embryonen [The Embryo Protection Act], Dec. 13, 1990, Federal Law Gazette (Part I, No. 69, Dec. 19, 1990, Bonn,) at 2746, sec. 8(1) (Ger.), *available at* http://www.hinxtongroup.org/docs/Germany2.html (last visited Feb. 13, 2015).
[18] Law on Ethics of Biomedical Research, Lietuvos Respublikos Seimas [The Seimas of the Republic of Lithuania], 11 May 2000 [As amended upto 15 Nov. 2007 – No X-1325], VIII-1679, art. 2(4) (Lith.).
[19] *Id.* art. 2(14).
[20] *Id.* art. 2(4), 2(14).
[21] 2005 Mass. Act § 2.
[22] According to Section 3(a) of the Act of 2005, "[r]esearch and clinical applications involving the derivation and use of human embryonic stem cells, including somatic cell nuclear transfer, human adult stem cells from any source, umbilical cord cells, parthenotes and placental cells shall be permitted." 2005 Mass. Act § 3(a).
[23] S.D. CODIFIED LAWS § 34-14-20 (2013), *available at* http://law.justia.com/codes/south-dakota/2013/title-34/chapter-14/section-34-14-20/ (last visited April 15, 2015).
[24] *Id.* § 34-14-16.

level of consciousness in the successive stages of fetal development. There are many definitions of the human embryo and it is hard to take one and say that, that one is perfect. Biology has prescribed certain stages of embryonic and fetal development but the legislations defined the human embryo quite differently from each other's.

Tania S. Bonny[25] commented on the diversity of prevalent legal definitions of "human embryo":[26]

> 1. Legal definition may or may not always conform to the current biological definitions. Sometimes they are simply not well updated as new knowledge is gathered. Some older legal definitions reflect older clinical/scientific definitions. Lithuanian law seems to be pretty recent compared to others and they have taken into consideration of the current medical definitions.
>
> 2. Legal definitions also take into account of other perspectives; apart from the biological/clinical context. The definition often reflects the prevailing thoughts and philosophy, culture, prejudice in a particular country or State.
>
> 3. In the absence of clinical expert comments, it is very unlikely that a layperson (or from different background) would be able to fully understand the clinical definitions. So, there is ample opportunity of coming up with different (legal) interpretations of the same definition/term for practical purposes. (In Dropbox with the researcher, April 17, 2015)

Therefore, the difference between the embryo and fetus is straightforward, i.e., "less than 8 weeks is embryo" and "more than 8 weeks is fetus" (weeks after fertilization). The debatable question is that, from which point after fertilization we should name the developing entity an "embryo." There are two school of thoughts:

a) Representing broad definition: embryo = from fertilization up to 8 weeks (Australian Government 2006, 3); and

b) Representing restricted definition: embryo = from 14-16 days post fertilization (from gastrulation stage) up to 8 weeks (Australian Government 2006, 4). Scientists from this school of thought refer to this first 14-16 days after fertilization as "embryogenic phase" (Australian Government 2006, 4). In this phase primitive streak is formed which separates the structure that forms the embryo from the extraembryonic tissues. Once they are separated after 14-16 days, the embryogenic (embryo generating) phase is complete and embryo development period starts (Australian Government 2006, 3--4). They like to call the entity during this 14-16 days (commencing from the fertilization) a "conceptus/pro-embryo/pre-embryo", and NOT an embryo (Australian Government 2006, 4).

Usually the broad definition is widely accepted and taught in clinical embryology and accordingly we have the UNSW Carnegie stages (Figure 2.1: "Human Development Timeline" (Illustration from UNSW Embryology: Human Development Timeline 2015)), i.e., Stage 1-23 = embryo and stage 24-onward= fetus.

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[25] Ph.D. Research Fellow (2013 – Onward), Dept. of Environmental & Global Health, University of Florida, USA; Lecturer, Dept. of Microbiology, University of Dhaka.

[26] I requested for an opinion on chapter 2.1 "CLARIFICATION OF THE KEY CONCEPTS IN THE RESEARCH CONTEXT".

Clearly, we can see that there is no consensus on when we should call an entity after fertilization an "embryo." This lack of consensus leaves room for different interpretations of embryo in the legal texts. Furthermore, how the legal definitions are formulated in accordance with the current knowledge and how different other perspectives (other than purely biological standpoint) are taken into consideration, make them (definitions/interpretations) even more diverse.[27] The diversity of interpretation is evident from the various sources stated above, i.e., litigations, Country/State laws, etc. This diversity of views/opinions/interpretations on embryo's definition also has implication/connection in patenting the hESC based inventions.

2.1.2 HUMAN STEM CELL BASED INVENTION/INNOVATION

In this monograph, wherever the acronym hSCI appears it shall mean the expressions "Human Stem Cell based Invention/Innovation." The terms "invention" and "innovation", despite synonymous have some differences. The primary intention of the "patent" is to offer IP protection for an invention. A *contribution* has to be able to differentiate itself from the mere "discovery," in order to apply for a patent. Some inventions neither completely represent the term "invention" nor "discovery," but they may make significant contribution to solve a technical problem. It is better to address those contributions as "innovation." Both the "invention" and "innovation" are different from mere "discovery." MacQueen et al. ([2008] 2010, 512) described: "While discoveries and inventions both contribute new knowledge to the sum total of human understanding, an invention does so through the *application* of that knowledge, for example, by making something available that was previously beyond our reach."

The "invention" solves the existing technical problems and hence it is novel and non-obvious for the purpose of patenting. But the "innovation" might not be very novel and could be just an up-gradation in the existing state of the art and hence, might be questionable from the perspectives of fulfilling the "non-obviousness" requirement of patenting. Life science embodies situations for both the "invention and innovation." I asked *Tania S. Bonny* [28] for an opinion on how *invention* and *innovation* occur in the process of hSCR. In her opinion:

> If you discover the genes encoding the specific transcription factors within the cell contributing to the character of *pluripotency*, this can be termed as an "innovation." The knowledge so acquired does not necessarily solve a problem but have long term impacts in the future research. You may develop a mechanism by which you are able to switch on these pluripotency associated genes in somatic cells (non-stem somatic cells do have these genes but they are switched off normally) and convert them to stem cells or behave like stem cells. One product derived using this approach is the induced pluripotent stem cells (iPSC). So, the iPSC can be termed as "an invention." It can be potentially used to treat diseases. Here both innovation and invention are based on stem cells or their properties. (Tania S. Bonny; In email with the researcher, May 30, 2014)

It is also necessary that the patented inventions show an "industrial application." Since the hSCI is a developing field of knowledge, many patented "claims" at this phase do not show any direct and

[27] In recent years, many developments took place in the reprogramming techniques, e.g., reprogramming by defined factors (Lewitzky and Yamanaka 2007, 467--473; Takahashi et al. 2007, 1--12).
[28] *Supra* note 25.

straightforward industrial application. Some of them will take long time to materialize the industrial application, although they were granted patents.[29] They can rather be termed as the "innovation," than "invention." If a technology has promising future application and is useful for subsequent downstream research, the term "innovation" is well suited for such discovery in life science. Some patents may have claims having the future applications and they can be also based on previous inventions. The inventions protected by some patents are not readily available as any therapeutic tool; rather they have future applications and contributions in improving the state of the art.

In the "Description" part of the U.S. Patent No. 8,759,098, issued on June 24, 2014 for the "[m]ethod for cloning pluripotent stem cells", assigned to Boston Biomedical Research Institute, Inc.[30] mentioned as "Background of Invention": "IPSCs derived from differentiated somatic cells of patients are potentially a powerful tool for biomedical research and may provide a source of cells for replacement therapies."[31]

The "Summary of the Invention" of the same patent (U.S. Patent No. 8,759,098, issued on June 24, 2014) provides the information about the discovery of this invention and its connections and reliance with other preceding inventions :

> Embodiments of the present invention are based on the discovery that adult stem cells expanded in culture by the method of suppression of asymmetric cell kinetics ("SACK;" e.g. See *U.S. Pat. Nos. 7,645,610; 7,824,912, and 7,655,465*) can be reprogrammed to undifferentiated (less differentiated) cells by culture in a cell growth media used for culturing embryonic stem cells (ESCs) in the absence of exogenous genes or proteins of the master transcription factors used for the *production of iPSCs*, i.e., Klf4, Oct3/4, c-Myc, Nanog, Lin 28, and Sox 2. In addition, embodiments of the invention are based on the discovery that *addition of xanthine* (Xn; the agent originally used to expand the adult stem cells by suppression of asymmetric cell kinetics) *to culturemedia* developed for the culture of pluripotent cells *increased the efficiency and speed* of production of iPSCs.[32] [Italics added]

The abovementioned patent will have implications for the subsequent researches and the invention itself is about improvisation of previous knowledge in the field. The background of the invention (U.S. Patent No. 8,759,098, issued on June 24, 2014) states that, "[t]he average success rate of producing iPSCs by the virus-mediate method is roughly one in 10,000 cells and takes about four weeks from start to finish."[33] The summary of this invention (U.S. Patent No. 8,759,098, issued on June 24, 2014) claims that, "[a]fter 2 weeks of culture in pluripotent stem cell culture medium, Xn-responsive expanded tissue stem cells become reprogrammed without any additional treatment with an efficiency comparable to methods that employ gene or protein transfer."[34] So, this patent (U.S. Patent No. 8,759,098)[35] claims to make iPSC in about "two" weeks instead of "four." Moreover, it does not suggest direct industrial application of the patent and it relied heavily on the preceding

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[29] By the time they will reach market, a substantial part of the "term of protection" may be lapsed.
[30] The inventor is James L. Sherley.
[31] United States Patent and Trademark Office, *USPTO Patent Full-Text and Image Database*, *available at* http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=%2Fnetahtml%2FPTO%2Fsrchnum.htm&r=1&f=G&l=50&s1=8,759,098.PN.&OS=PN/8,759,098&RS=PN/8,759,098 (last visited July 27, 2015).
[32] *Id.*
[33] *Id*.
[34] *Id.*
[35] Issued on June 24, 2014. *Id.*

inventions. Such process patents based on “methods” may be better suited if they are called “innovation.” These patented processes may contribute in overall iPSC production methodology but they are not substantial enough to be called “invention,” if the requirements of the patentability are understood strictly. But once they are patented, they automatically become “invention,” as the patent protects inventions only.

CHAPTER 3

HUMAN STEM CELL RESEARCH AND INVENTION: ANALYSIS OF ETHICAL AND LEGAL ISSUES

3.1 HUMAN STEM CELL RESEARCH: VARIOUS TYPES AND THEIR ETHICAL AND LEGAL ISSUES

The Health and Safety Code of California defined and described human Stem Cell (hereinafter referred to as hSC) as, "nonspecialized cells that have the capacity to divide in culture and to differentiate into more mature cells with specialized functions."[1] This sub-chapter (3.1) of the monograph discusses various scientific, ethical and legal issues concerning the human Stem Cell Research (hereinafter referred to as hSCR). The following types of hSCR and the techniques of the derivation of hSC have been examined from the clinical, ethical and legal perspectives in this chapter:

- Adult Stem Cell;
- hESC (Human Embryonic Stem Cell) from ICM of the Blastocyst;
- NT-ESC/SCNT (Somatic Cell Nuclear Transfer);
- iPSC (Induced Pluripotent Stem Cell);
- ESC (Embryonic Stem Cell) from the Blastomere Cell (Extracted by embryo biopsy);
- hpSC ((Human Parthenogenetic Stem Cell) By parthenogenetic activation of eggs);

Following classification of the hSC researches is made for the purpose of the discussion:

A. Human *multipotent* stem cells, i.e., the adult stem cells, somatic cells; and

B. Human *pluripotent* stem cells, i.e., human Embryonic Stem Cell (hereinafter referred to as hESC) and induced Pluripotent Stem Cell (hereinafter referred to as iPSC), etc.

This classification of human cells is done from the perspectives of the cell potency. Although the hESC and iPSC are grouped as *pluripotent* for the purpose of the discussion, they have notable differences and resemblances which are discussed throughout this sub-chapter.

[1] CAL. HEALTH & SAFETY CODE § 125292.10 (x) (West 2012).

The following figure published by Shoukhrat Mitalipov and Don Wolf (2009) shows the cell potency and how the reprogramming techniques create the cells with differing degree of *potency* at the different stages of the development of human organism.

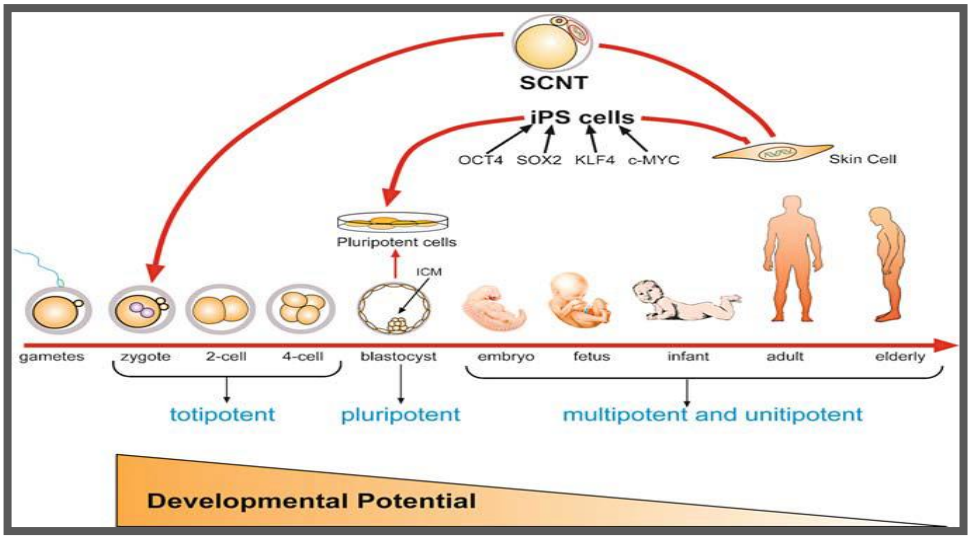

Fig. 3.1 "Development and reprogramming." (Figure 1, Mitalipov and Wolf 2009, 12)

3.1.1 ADULT STEM CELLS AND SOMATIC CELLS

Stem cells and its various derivation techniques can be better understood from the description of their methods, rather than from any confined definition. The California Institute for Regenerative Medicine described the features of the adult stem cells as following: "These [adult stem cells] are specialized cells found in tissues of adults, children and fetuses. They are thought to exist in most of the body's tissues such as the blood, brain, liver, intestine or skin." (California Institute for Regenerative Medicine: Stem Cell Definitions 2014). Adult stem cells are also the most constrained one in terms of cell potency, differentiation and application if compared with ESCs. They can repair the tissues of their own kind, i.e., the kind from which they were extracted (NIH Stem Cell Information 2013). This is why they are called "tissue-specific stem cells" (California Institute for Regenerative Medicine 2013); and they are not capable to form any other kind of tissues of the body. Therefore, the adult stem cells are the undifferentiated cells that have the potential to give rise to other somatic (body) cells (which are fully differentiated cells) and new stem cells so that they can continue to replenish and repair the tissue from where they originated. The somatic or body cell[2] has been a good ingredient for producing *pluripotent* stem cells by direct reprogramming through transcription factors (iPSC) or through Somatic Cell Nuclear Transfer. Research on adult stem cells attract the least debates for their source and process of extraction. However, adult stem cell has some potential and application, of course, e.g., in oncology treatments (Sipp 2011, 275--286).

[2] Germ cells i.e., sperm and egg cells are not somatic cells (NIH Stem Cell Information 2013). Adult human body has the following two basic types of cells in terms of the chromosome copy they carry:
a) Somatic cells of all types: Each of these cells carry double copy of each chromosome (DNA are present in thread-like structures called the chromosomes). So, every gene is present in "double copy"; and
b) Germ cell: Egg and sperm are the only germ cells in the body. These cells carry single copy of each gene. So, when a zygote is formed, it receives a single copy of the same chromosome from both the egg and sperm. Then the zygote becomes double chromosome copy again. Moreover, this amalgamation of chromosome from two different sources is the reason why a *baby* acquires some features of the *mother* and some from the *father*.
The Somatic or body cells are of two types:
1. Fully differentiated somatic cells; and
2. Undifferentiated adult stem cells.

3.1.2 HUMAN PLURIPOTENT STEM CELLS

The *pluripotent* stem cells have the capacity to differentiate into almost all cell types of the body. The *pluripotent* stem cells can be generated from embryonic and non-embryonic sources. This classification of stem cell as human Pluripotent Stem Cell (hereinafter referred to as hPSC), is a classification from the perspective of cell potency, not from the source of extraction. As of its own, hPSC is not a specific type of stem cell. It is rather a classification or identification of those cells that possess the particular level of differentiation capacity called "*pluripotency*".

3.1.2.1 EMBRYONIC STEM CELLS

The ESCs were first derived by the team of James A. Thomson (Thomson et al. 1998). They were derived from the *totipotent* cells at the early stage of embryonic development and showed "high levels of telomerase activity" which is associated to rejuvenation of cell lines (Thomson et al. 1998, 1145). The study reported immense capacity of differentiation of the embryonic stem cell but reported *teratoma* formation in the mice (Thomson et al. 1998, 1146--1147).

The hESCs can be derived both from the *totipotent* and *pluripotent* sources.[3] The *totipotent* cells are derived at the earliest stage of the embryonic development, i.e., until the 8-cell stage (Intellepro IP management: Stem Cells 2014).[4] But there is higher degree of legal constraint and ethical objections in derivation of *totipotent* cells, as these cells are capable of producing the live birth.[5]

[3] The possible derivation of the stem cells from the *totipotent* or *pluripotent* sources directs to two different stages of human (mammalian in general) development:
First, the egg fertilized by sperm becomes one cell zygote. Zygote is *totipotent* and remains so until it divides up to at least 4-cell stage called "blastomeres" (Mitalipov and Wolf 2009, 2); and
Second, further cell division occurs and cells become more mature structure called "blastocysts." Blastocysts has two components namely the "inner cell mass (ICM)" and "trophectoderm (TE)." The *pluripotent* stem cells can be obtained from the ICM of the blastocyst and the *totipotent* stem cells can be derived from until at least the 4-cell stage (Mitalipov and Wolf 2009, 2).

[4] 4-8 cell stage, varies in different cited sources.

[5] Shoukhrat Mitalipov and Don Wolf while explaining "*totipotency*" narrated that: "each totipotent cell is a self-contained entity that can give rise to the whole organism. This is said to be true for the zygote and for early embryonic blastomeres up to at least the 4-cell stage embryo" (2009, 2).
They are called "*totipotent*" because they can give rise to a total organism. As *totipotent* cells can give rise to complete blastocysts (which is comprised of the Inner Cell Mass (ICM) and trophectoderm (TE)), they are capable of live birth. In contrast, stem cells derived from ICM are *pluripotent* because the blastocyst is destroyed when the stem cells are derived from the ICM. The ICM devoid of trophectoderm (TE) is incapable of live birth. Because the TE makes the placenta which is integral to the fetal development.

Generally, human embryonic *pluripotent* stem cells are collected from until about the fifth day of the embryonic development after the fertilization (California Institute for Regenerative Medicine: Stem Cell Definitions 2014). This commonly practiced derivation of ESCs results in the destruction of the embryo/pre-embryo[6] from which the cells are extracted.

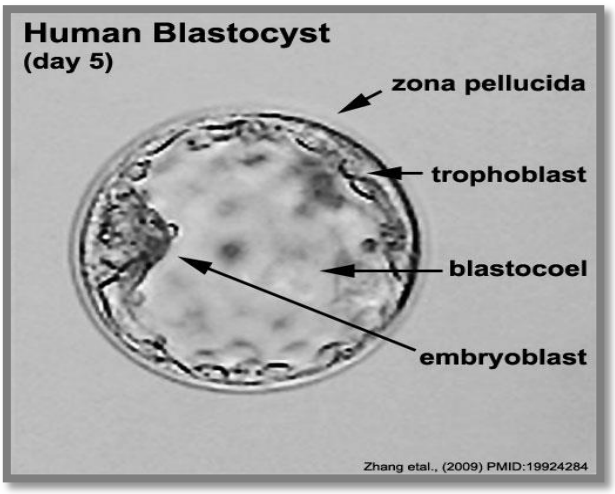

Fig. 3.2 Human Blastocyst on Day 5 (Figure 4, Zhang et al. 2009, 5; Illustration from UNSW Embryology: Blastocyst Development 2014)

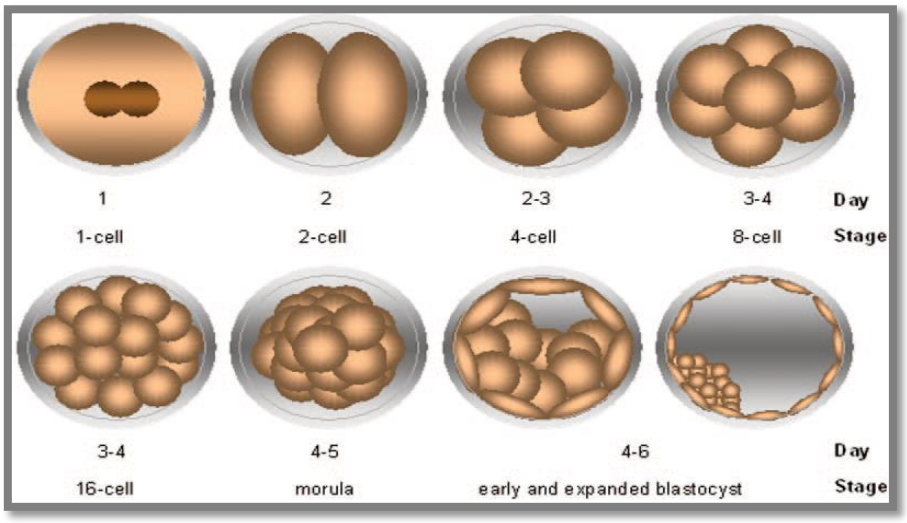

Fig. 3.3 "Developmental stages and chronological time of normal early human development up to blastocyst stage. […]. These embryos cleave to morulae on Day 4 and to blastocysts on Day 5." (Figure 1, Zhang et al. 2006, 2670)

[6] The embryonic entities from which the *pluripotent* cells are derived, are termed as "embryo" or "pre-embryo." Since there is no conclusive scientific definition of embryo, the terminology depends on the legal text of the individual State.

3.1.2.2 REPROGRAMMING BY SOMATIC CELL NUCLEAR TRANSFER AND THE DIRECT INTRODUCTION OF TRANSCRIPTION FACTORS

The iPSC is a *pluripotent* stem cell generated from the non-embryonic sources. Yu et al. (2007) and Takahashi et al. (2007) reported about the reprogramming of somatic cell into *pluripotent* stem cell that resemble the embryonic (human) stem cells. Yu et al. (2007)[7] used OCT4, SOX2, NANOG and LIN28 genes and Takahashi et al. (2007)[8] used Oct3/4, Sox2, c-Myc and Klf4 genes as the "transcription factor" for the reprogramming of the adult human cells into the state of *pluripotency*. The variation in reprogramming and the diverse approaches of producing the *pluripotent* stem cells by scientists can be observed from the recent publications.

Before the direct reprogramming of the somatic cells to iPSC was invented by Takahashi and Yamanaka (2006), the most typical technique for therapeutic cloning existed is the SCNT procedure. The SCNT technique involves fusion of the adult somatic cell nucleus with the enucleated egg of the donor. John B. Gurdon employed the SCNT procedure to produce viable "frog" in 1962 (Gurdon 1962; Nobelprize.org.: Sir John B. Gurdon – Facts 2015), which is also the earliest successful example of cloning. Shoukhrat Mitalipov and his team claimed to have successfully cloned human embryos by employing an optimized SCNT protocol adapted to human (Tachibana et al. 2013). It is a modified SCNT protocol which is uniquely suited to produce ESC from human somatic (dermal fibroblast) cells and egg (oocyte) donated by healthy volunteers (Tachibana et al. 2013). The previous SCNT protocols involved amphibians (frog) and non-human primate model and had not been successful in human experimentation. Tachibana et al. (2013, 1228) claimed that, "the derivation of human nuclear transfer-embryonic stem cells (NT-ESCs) has not been achieved despite numerous attempts during the past decade." This team came up with a modified SCNT protocol exclusively for human and produced good quantity of ICM. Masahito Tachibana et al. (2013, 1231) reported : "[I]ncorporation of caffeine [a protein phosphatase inhibitor] during enucleation and fusion allowed improved blastocyst development and ESC line derivation."

[7] The team is known by the name of James A. Thomson.
[8] The team is known for Shinya Yamanaka.

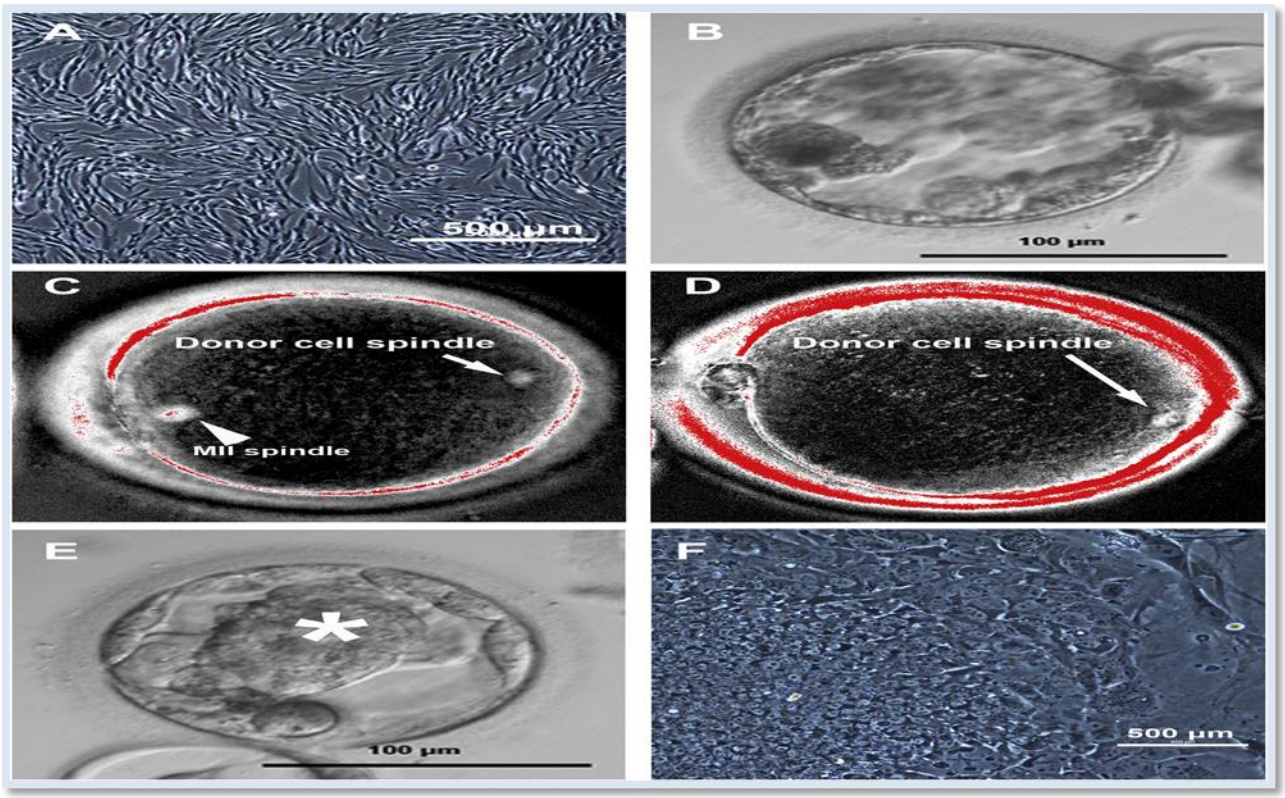

Fig. 3.4 "SCNT Blastocyst Development Is Affected by Premature Cytoplast Activation [….]. (F) NT-ESC colony with typical morphology derived from a caffeine-treated SCNT human blastocyst." (Figure 2, Tachibana et al. 2013, 1230)

The SCNT technique was also applied to produce the sheep "Dolly" in 1996 (Wilmut et al. 1997). By using the SCNT procedure, the sheep "Dolly" was the first mammal to have been cloned from the adult somatic cell (Wilmut et al. 1997). But in that case, the embryo was brought to full term. On the other hand, Mitalipov team's goal was to produce mature blastocysts with abundant ICM so that the ESC can be derived. This procedure is also describable as "human cloning" but the embryo was not brought to term; rather the hESCs were derived from the blastocyst stage by halting the development of the embryos grown in vitro.

Both the SCNT and iPSC are used to generate cells that resemble and act like ESC, i.e., exhibiting the property of *pluripotency*, but the approaches are different. For the SCNT, through nuclear reprogramming, the nucleus of a somatic cell is inserted into an enucleated egg[9] and allowed to propagate (Tachibana et al. 2013; Li et al. 2009; French et al. 2008). The resulting clone may develop into an embryo. Jianyuan Li et al. (2009, 43) published the "[d]evelopment of […] human embryo derived from SCNT".

[9] Egg without its own nucleus.

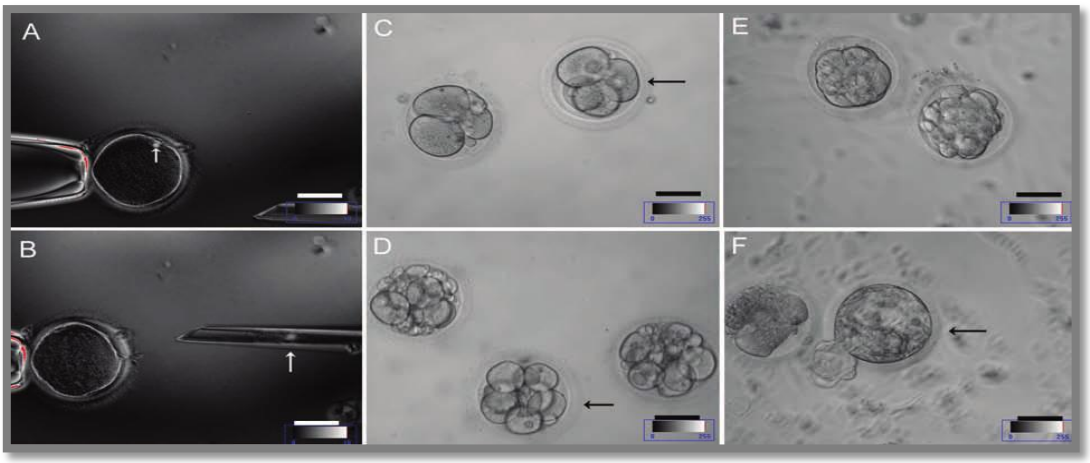

Fig. 3.5 "Development of a human embryo derived from SCNT. […]. (C) Four-cell stage. (D) Eightcell stage. (E) Morula. (F) Blastocyst." (Figure 2, Li et al. 2009, 43)

The SCNT technique can be applied in two ways:

a) Reproductive cloning, i.e., the embryo is implanted into a uterus and brought to term. The reproductive cloning (of human) is largely prohibited for ethical reasons.

b) Therapeutic cloning through the destruction of the embryo to derive the ESCs for research and therapeutic purposes.

The following diagram of Paul Knoepfler ((2013); Knoepfler Lab Stem Cell Blog 2014) depicts the therapeutic and reproductive cloning:

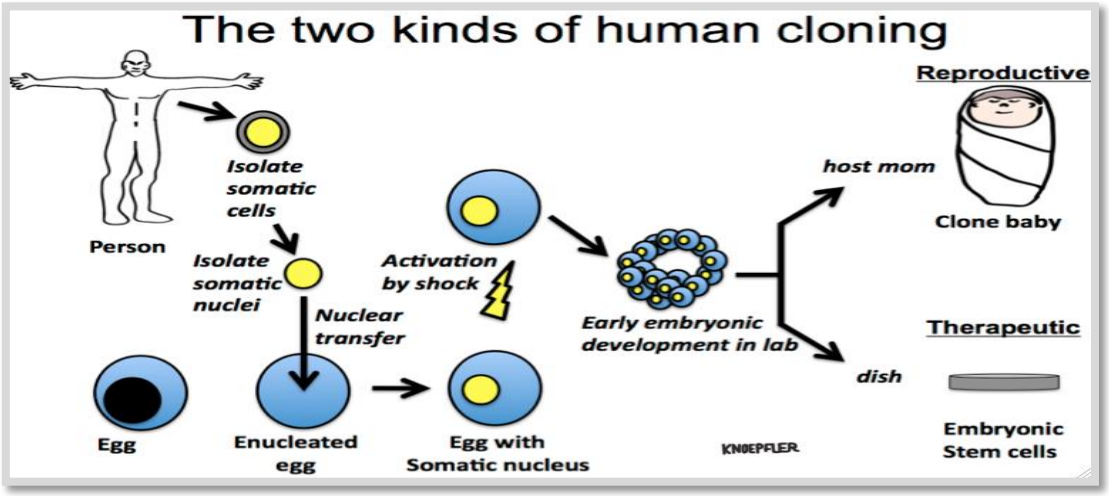

Fig. 3.6 Human SCNT Cloning Options (Illustration from Knoepfler 2013, 299--300; Knoepfler Lab Stem Cell Blog 2014)

The SCNT has three major concerns (ethical and clinical):

(i) it requires healthy eggs;[10]

(ii) the efficiency is low;

[10] Tachibana et al. (2013, 1235) reported: "[T]he oocyte quality is ultimately linked to the genetic constitution of individual egg donors."

(iii) it causes destruction of the embryo to derive the ESCs used for research and therapy.

The iPSC technology emerged in 2006.[11] These cells were generated through direct nuclear reprogramming of somatic cells by introducing the transcription factors (Takahashi and Yamanaka 2006). This technology does not involve any egg and embryo production and their subsequent destruction. Instead, the technique of generating iPSC employs only somatic or adult stem cell and a direct reprogramming of that somatic cell is performed to achieve an ESC-like cell. Therefore, the iPSC technology has no concern around *egg donation* and *embryo destruction* but it has concerns over the *efficiency* of production and *safety* in application. However, safety in application is a concern for all therapeutic applications stemming from all the emerging stem cell technologies. Christine L. Mummery and Bernard A. J. Roelen (2013) made a comparative discussion of the iPSC generation reported by Takahashi and Yamanaka (2006) and SCNT procedure by Tachibana et al. (2013). The differences between the two reprogramming are stated in the words of Mummery and Roelen as follows:

> In iPS cells, mitochondria (organelles that are the main source of cellular energy), as well as all other organelles, originate from the donor cell. In SCNT-ES cells, the mitochondria are derived from the oocyte and not from the donor of the nucleus. Apart from the nucleus, mitochondria are the only organelles that contain DNA, which encodes around ten genes. This means that SCNT-ES cells might activate the immune system of an individual who is ostensibly being treated with their 'own' SCNT-ES cells and cause them to be rejected. [….] Direct reprogramming of human iPS cells takes several weeks, whereas SCNT-ES cells are reprogrammed within a few hours by the natural factors present in the oocyte, and could in principle give rise to new offspring. (Mummery and Roelen 2013, 174--75)

However, in addition to the above discussion Mummery and Roelen (2013) drew an eloquent comparative diagram of the both reprogramming techniques.

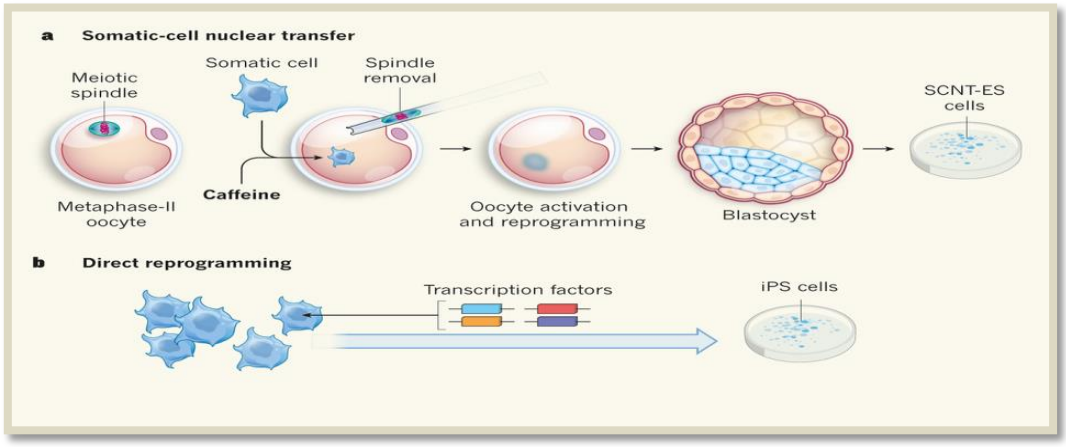

Fig. 3.7 Diagram of SCNT (NT-ESC) of Tachibana et al. (2013) ("a"), and iPSC of Takahashi and Yamanaka (2006) ("b") (Figure 1, Mummery and Roelen 2013, 174)

[11] The first invention of its kind involved the reprogramming of the mouse somatic cells.

However, could the cloning of embryo by the team of Mitalipov (Tachibana et al. 2013) raise the concern of live birth of human? How different the technique is from the reproductive cloning? The scientist taking part in the study negated the chance of live birth by claiming that they tried this on monkeys and it did not produce live birth (Cyranoski 2013, 296). However, it appears that Mitalipov team destroyed the mature blastocysts and collected ICM from them. It is pertinent to mention that two things are required to produce a live birth:

1. An intact and viable blastocyst which has both ICM and TE (Trophectoderm);[12]

2. A living female uterus where this blastocyst will be implanted.[13]

What they did is the completion of the first step of cloning (which is common protocol/step for both reproductive and therapeutic cloning) but they did not proceed towards placing the cloned embryo in the uterine environment (which is the further step towards the reproductive cloning); instead they destroyed the blastocyst and derived ESCs. The Mitalipov team followed the procedure towards the goal of the therapeutic cloning and did not proceed further towards the goal of reproductive cloning, after cloning the embryos.

One of the core ethical objections against ESC research is that the destroyed embryo had a potential to become life. The deliberate destruction or certain use of embryos for commercial purposes, is the ethical concern, for certain school of moral philosophy. Do the iPSC and SCNT raise same or similar concern? The SCNT involves production of embryo to derive the ESCs. If the developing embryos (cloned embryos) were implanted in the optimal environment (conventionally within a uterus),[14] those embryos might have the potential to live birth. But the legal framework in order to approve or reject such research must make an objective evaluation of scientific integrity, ethics and potential application of those embryos. Customized therapy targeting specific patient may require the donation of egg and adult somatic cells from that patient. In this case an embryo will be made using SCNT destined to "destruction," solely because it was made with an intention to prepare the stem cell therapy.

Takahashi et al. (2007) reported the success of direct reprogramming of somatic cell into iPSC (human) by transcription factors. Wernig et al. (2007) published that, "iPS cells can establish all lineages of the embryo and thus have a similar developmental potential as ES cells."[15] Several researches found birth of mice from "several iPS cell lines" by "tetraploid complementation" possible (Zhao et al. 2009; Kang et al. 2009). Therefore, the claim by Wernig et al. (2007) stating

[12] Without the TE and the external cell layer, the placenta can not be produced.

[13] The placenta connects maternal circulation to the embryo. An embryo cannot develop if it is not placed in uterine environment and so it has to remain connected to the mother through the placenta during the entire period of fetal development until the birth.

[14] There are legal restrictions regarding the development of an embryo outside of human body. For example, section 3(3)(a) of the Human Fertilisation and Embryology Act, 1990 of UK prohibits "keeping or using an embryo after the appearance of the primitive streak" and that limit is clarified as until the 14th day from the fertilization in section 3(4) of the same Act. Human Fertilisation and Embryology Act 1990, *available at* http://www.legislation.gov.uk/ukpga/1990/37/section/3 (last visited Feb. 05, 2015). It means that even in UK, which offers the most pragmatic legal framework in embryo related research, the human embryo cannot be developed outside of human uterus after the 14th day of fertilization. The normal practice of post IVF (In Vitro Fertilization) embryo implantation serves the reproductive purpose only. For research and experiment, no human uterus is used and the legal restrictions do not seem to be flexible enough to by-pass. For example section 3(2)(a) of the Human Fertilisation and Embryology Act 1990 of the UK states that "[n]o person shall place in a woman a live embryo other than a human embryo." Human Fertilisation and Embryology Act 1990, *available at* http://www.legislation.gov.uk/ukpga/1990/37/section/3 (last visited Feb. 05, 2015). For the reproductive purpose, the IVF (In Vitro Fertilization) embryos are not prepared through nuclear reprogramming. They are fertilized *in-vitro* by fusing the egg and sperm cell and implanted into the uterus (NYU Fertility Center: About the In Vitro Fertilization (IVF) Process 2014).

[15] That experiment was performed in mouse.

that "somatic cells can be reprogrammed to a pluripotent state that is similar, if not identical, to that of normal ES cells", is quite acceptable. These studies indicate that human iPSC has a potential to contribute to a live birth, only if the *tetraploid complementation assay* is followed. It is important to mention that *tetraploid complementation assay* is used to test the *pluripotency* and developmental potential of the iPSCs; it is not an essential or integral procedure for the therapeutic application of the iPSC. For the therapeutic application, what will be needed is that the iPSC is reprogrammed efficiently and properly so that its achieved *pluripotency* can contribute to the desired therapeutic purpose. In case of iPSC, a somatic cell is directly reprogrammed to ESC-like cell and it does not involve embryo formation in order to go for therapeutic application. Therefore, the iPSC (that would be used for the therapy) itself does not have the direct "potential to life."[16]

Therefore, if the potentiality of live birth, i.e., the "potential to life" is an ethically unacceptable situation for ESCs research, it may concern SCNT/NT-ESC more directly. In the process of the stem cell derivation, the difference between hESC (the one derived from the ICM of the Blastocyst) and NT-ESC (SCNT) is that:

- the hESC (from ICM of the Blastocyst) would destroy an embryo (from the germ cell) that had a potential to life; and
- the NT-ESC (SCNT) would destroy a "cloned embryo" (from the somatic cell) the potential of which is presumed, not decisively established yet.

If compared between the iPSC and embryo cloning by SCNT (NT-ESC), the iPSC may be more acceptable than SCNT on ethical ground, because the embryo production using healthy egg is an indispensable step for SCNT. Requirement of healthy eggs and their supply for the lab would just not be limited to donation, if this technique becomes popular. David Cyranoski (2013, 296) reported: "Egg donors for the [Mitalipov's] experiment received US$3,000-7,000 in compensation."

The diverse choices of the respondents can be observed from their opinion on "human embryo destruction" in response to the question no. 3.[17] Following are the *Major Key Themes* derived from responses to question no. 3:[18]

- Unethical in general;
- Acceptable to employ embryo in limited circumstances;
- Balance of rights;
- Contribution of the research to the society and the individual;
- Support for only the use embryos in research that are redundant for clinical purposes (e.g., IVF);
- The creation of *in-vitro* embryo exclusively for research purposes considered unethical;
- Proportion and reality;

[16] Some authors argue that having potential does not mean anything by itself, until it is realized into reality (Devolder 2009, 1285).

[17] Question No. 3 says: "How do you see the act of destruction of human embryo for the purpose of research and invention/innovation".

[18] Some of the words/phrases used/mentioned within quotation in the major key themes and their interpretations are the exact words/phrases used by the respondents. Appendix V: Qualitative Analysis (Qualitative Content Analysis (QCA)).

The questionnaire mentioned that, "the identity of the participants shall be kept anonymous, unless required to prove the authenticity of the study." Appendix II: Questionnaire.

- The "term 'embryo' lacks definition";
- The word "destruction" has a negative connotation;
- Embryo at early stage is a "biological material of human origin" and a different component from the human being or human body;
- Alternative sources are available;
- Cord blood cells can provide the same types of stem cells;
- Good scientific rationale, informed consent from embryo donors and careful monitoring are critical.

The Interpretation of the *Major Key Themes* derived from responses to question no. 3 can be found in Ch. 5.

3.1.2.3 STEM CELLS DERIVED FROM THE PRE-IMPLANTATION STAGE EMBRYO'S BLASTOMERE CELL, HUMAN PARTHENOGENETIC STEM CELLS, ETC.

Irina Klimanskaya et al. (2006, 481) reported the derivation of embryonic stem cell "from single blastomeres."

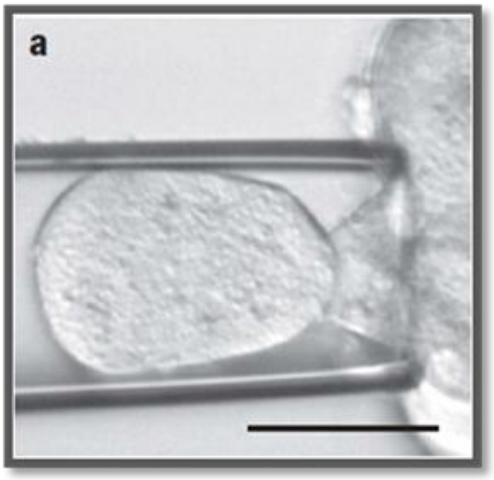

Fig. 3.8 "Derivation of hES cells from single blastomeres. a, Biopsy of a single blastomere." (Figure 1, Klimanskaya et al. 2006, 482)

The United States Patent Number 7,893,315, issued on February 22, 2011 was assigned to Advanced Cell Technology, Inc. of Marlborough, Massachusetts, USA[19] for the methods of derivation of human embryonic stem cells from 8-cell stage embryo through blastomere cell removal without causing destruction of the embryo's normal developments (Advanced Cell technology: Research &Development 2014).[20] Another patent[21] recently granted to the same group of inventors and

[19] Advanced Cell Technology has changed its corporate name to "Ocata Therapeutics, Inc." on November 14, 2014 (Ocata Therapeutics, Inc.: Advanced Cell Technology Changes Name to Ocata Therapeutics 2014).
[20] The inventors are Young Gie Chung, Robert Lanza and Irina V. Klimanskaya.
[21] U.S. Patent Number 8,742,200 (issued June 3, 2014).

assignee[22] for the "[d]erivation of embryonic stem cells and embryo-derived cells" mentioned in the "summary of the invention" the following features of the inventions:

> The ES cells produced from the blastomere may be pluripotent or by some definitions totipotent.[….]. The embryo may be from the 2-cell stage to the 16 cell stage. In one embodiment, the embryo is from the 4 cell stage to the 10 cell stage. In another embodiment the embryo is a 6-8 cell stage embryo. In yet another embodiment, the embryo is an 8-10 cell stage embryo. (U.S. Patent Number 8,742,200; issued June 3, 2014)

Since some of the derived cells are *totipotent* by some definitions, the derived *totipotent* cells may have the "potential to life" (if provided with a conducive environment), given the fact that only *pluripotent* cells cannot culminate into live birth for lacking the ability to form the extraembryonic tissue. Another ethical concern for this method is that the process *may* undermine the *safety of the biopsied embryo, if it is implanted* after the extraction of the blastomere cell. Stem cell can be propagated from the *blastomere cell taken out* from a pre-implantation embryo (in conjunction with IVF; similar to PGD) and it is claimed in the "[d]escription of the invention" that the remaining part of the developing embryo can be successfully implanted into the uterus.[23] The "summary of the invention" of the United States Patent No. 8,742,200, issued on June 3, 2014 states:

> "In another aspect, the invention provides a method of generating autologous stem cells concomitantly to performing genetic diagnosis. A blastomere is removed from an embryo, as is typically done during pre-implantation genetic diagnosis (PGD). The blastomere is cultured and permitted to divide at least once. After division, one progeny cell is used for genetic diagnosis, and the other progeny cell is further cultured (using any of the methods described herein) to produce an ES cell or ES cell line."[24]

The description of the invention of United States Patent No. 8,742,200, issued on June 3, 2014 states that, "[i]n one embodiment the invention provides methods for biopsy of a blastocyst which will produce embryonic stem cells, and the remainder of the blastocyst is implanted and results in a pregnancy and later in a live birth."[25] Is it scientifically established that, *that an implanted embryo brought to term*[26] did not have any *developmental abnormality* that might affect the quality of life of

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[22] The assignee is the Advanced Cell Technology, Inc. (Marlborough, MA) and the inventors are Young Gie Chung, Robert Lanza and Irina V. Klimanskaya.

[23] United States Patent and Trademark Office, *USPTO Patent Full-Text and Image Database*, *available at* http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=%2Fnetahtml%2FPTO%2Fsrchnum.htm&r=1&f=G&l=50&s1=8,742,200.PN.&OS=PN/8,742,200&RS=PN/8,742,200 (last visited June 23, 2015).

[24] United States Patent and Trademark Office, *USPTO Patent Full-Text and Image Database, available at* http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=%2Fnetahtml%2FPTO%2Fsrchnum.htm&r=1&f=G&l=50&s1=8,742,200.PN.&OS=PN/8,742,200&RS=PN/8,742,200 (last visited Mar.17, 2015).

[25] United States Patent and Trademark Office, *USPTO Patent Full-Text and Image Database*, *available at* http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=%2Fnetahtml%2FPTO%2Fsrchnum.htm&r=1&f=G&l=50&s1=8,742,200.PN.&OS=PN/8,742,200&RS=PN/8,742,200 (last visited Nov. 27, 2014).

[26] No published report of successful "implantation" and "live birth" was found corresponding (related to) to this assay/method; only the possibility (as a method) is claimed/stated. The "summary of the invention" of the United States Patent No. 8,742,200, issued on June 3, 2014 states: "The biopsied embryo may be implanted or cryopreserved." United States Patent and Trademark Office, *USPTO Patent Full-Text and Image Database*, *available at* http://patft.uspto.gov/netacgi/nph-

the resulting child/human? What are the short or long-term consequences in the *human* born from a biopsied embryo? Embryo biopsy is usually conducted for the PGD. In the case of PGD, the same thing is done but with a *different objective*. For PGD a single blastomere cell is taken out and tests are conducted to find out any genetic abnormality that may be harmful for the optimum "embryo development." There is still concern and question as to how safe and effective PGD is to ensure that a healthy baby with *normal genetic makeup* would be born?

Richard Sherbahn MD[27] wrote: "[M]ore studies on PGD for aneuploidy screening are needed. […]. Studies are needed for both day 3 biopsies with fresh embryo transfers and day 5-6 biopsies with frozen embryo transfers with evaluation of all 23 chromosomes" (Advanced Fertility Center of Chicago: PGS and IVF - Preimplantation Genetic Screening Using Day 3 Embryo Biopsy 2015).

Those parents who have real concerns that some genetic abnormalities might be transferred to the offspring unless something is done to prevent it, mostly request that PGD procedure.[28] This "stem cell derivation process" is not employed under the belief that the embryo itself might have some diseases that need to be prevented or addressed. Moreover, *early stage (2-16 cell)*[29] *embryos* are used/biopsied for this technique.[30] The objective of this method seems to *derive ES cell without destroying the developmental potential of the embryo*.[31] The US patent No. 8,742,200, issued on June 3, 2014 stated as "Methods of Conducting Research":

> "As detailed above, embryonic stem cell research has been partially hindered by political and ethical opposition to the destruction of embryos. The present invention not only provides an alternative method for efficiently generating cells and cell lines, including ES cells and cell lines, the present invention also provides a method that does not require that new embryos be destroyed as part of the process of ES cell derivation. Remaining embryos can be cryopreserved and perpetually preserved or reserved for additional, future research use.[32]

Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=%2Fnetahtml%2FPTO%2Fsrchnum.htm&r=1&f=G&l=50&s1=8,742,200.PN.&OS=PN/8,742,200&RS=PN/8,742,200 (last visited June 25, 2015).

Chung et al. (2008, 113) successfully grew the biopsied embryos to the blastocyst stage and froze them down. It was NOT proven/claimed that these cryopreserved blastocysts were later implanted and resulted in successful birth without any developmental defect/abnormality in the embryo/resulting child.

[27] Program Director of the Advanced Fertility Center of Chicago.

[28] However, there are some reports of PGD increasing the rate of successful IVF (Gianaroli et al. 1997, 1128; Sher et al. 2009, 1886).

[29] U.S. Patent Number 8,742,200, issued on June 3, 2014 states in the "summary of the invention": "The embryo may be from the 2-cell stage to the 16 cell stage." United States Patent and Trademark Office, *USPTO Patent Full-Text and Image Database, available at* http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=%2Fnetahtml%2FPTO%2Fsrchnum.htm&r=1&f=G&l=50&s1=8,742,200.PN.&OS=PN/8,742,200&RS=PN/8,742,200 (last visited June 26, 2015).

[30] Chung et al. (2008, 115) reported: "An experiment was carried out with blastomeres removed from two frozen cleavage-stage embryos that were thawed and cultured in blastocyst medium for 2 hr prior to biopsy."

[31] The "abstract" of the United States Patent No. 8,742,200, issued on June 3, 2014 states: "This present invention provides novel methods for deriving embryonic stem cells and embryo-derived cells from an embryo without requiring destruction of the embryo." United States Patent and Trademark Office, *USPTO Patent Full-Text and Image Database, available at* http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=%2Fnetahtml%2FPTO%2Fsrchnum.htm&r=1&f=G&l=50&s1=8,742,200.PN.&OS=PN/8,742,200&RS=PN/8,742,200 (last visited June 18, 2015).

[32] United States Patent and Trademark Office, *USPTO Patent Full-Text and Image Database, available at* http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=%2Fnetahtml%2FPTO%2Fsrchnum.htm&r=1&f=G&l=50&s1=8,742,200.PN.&OS=PN/8,742,200&RS=PN/8,742,200 (last visited June 19, 2015).

How does "cryopreservation" works as substitute of the "destruction" of the embryo to console the ethical controversies around the latter? The US patent No. 8,742,200, issued on June 3, 2014 stated in the "Therapeutic Uses of ES and ED Cells" (as the description of the invention):

> In one embodiment the methods of the invention are used to remove a blastomere *preceding implantation of a human embryo* after which the blastomere would be cultured as described above in order to derive and store human ES cells for therapeutic uses using cell therapy should the child resulting from the human embryo require, for example, disease therapy, tissue repair, transplantation, treatment of a cellular debilitation, or treatment of cellular dysfunctions in the future.[33] [italics added]

How do we know in advance that the resulting child/human might need ES cells in future? Ethical concern may persist, if an embryo is *biopsied, stem cells derived and later implanted*. However, Klimanskaya et al. (2006, 484; nn. omitted) mentioned: "Numerous reports suggest that neither the survival rate nor the subsequent development and chances of implantation differ between intact human embryos […] and those following blastomere biopsy for PGD. However, until remaining doubts about safety are resolved, we do not recommend this procedure be applied outside the context of PGD."

In 2001, Jose B. Cibelli et al. reported parthenogenetic[34] activation of human eggs and demonstrated a "protocol for parthenogenetic activation of human eggs, embryonic cleavage, and the formation of a blastocoele cavity" (Cibelli et al. 2001, 29). Brevini and Gandolfi published that parthenotes[35] created by parthenogenesis may be alternative source of the *pluripotent* stem cells (2008, 20--30). They claimed that the parthenotes created do not develop to the full term (Brevini and Gandolfi, 2008, 21).

The United States Patent Application No. 20140234968, published on August 21, 2014 claimed to have optimized both the pn-hPSC[36] and NT-hPSC[37] procedures.[38] They claimed to have achieved the following:

1. pn-hPSC through parthenogenesis: They found these stem cell lines to be immunocompatible to a broad category of patient population (i.e., being able to match to a wide range of patients with differing HLA histocompatibility);[39] and

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[33] *Id.*

[34] Brevini and Gandolfi (2008, 21) described: "Parthenogenesis is the process by which a single egg can develop without the presence of the male counterpart and is a form of reproduction common to a variety of organisms such as fish, […], lizards and snakes[…]."
Parthenogenetic development does not naturally occur in the reproductive process of the mammalian species and therefore, human organism's development in this process is not a naturally occurring phenomenon.

[35] In both the papers (Brevini and Gandolfi 2008; Cibelli et al. 2001) the end product is the same. Brevini and Gandolfi (2008) used the term "parthenotes" in their review paper, while Cibelli et al. (2001) named it "autologous embryo". However, their strategy of parthenogenetic egg activation is slightly different.

[36] Parthenote Derived Human Pluripotent Stem Cells.

[37] Nuclear Transfer Human Pluripotent Stem Cell.

[38] United States Patent Application 20140234968, published on August 21, 2014 having Young Gie Chung and Dong Ryul Lee as the inventors and Sung Kwang Medical Foundation, Seoul, Korea as the applicant and assignee. United States Patent and Trademark Office, *Patent Application Full-Text and Image Database, available at* http://appft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PG01&p=1&u=%2Fnetahtml%2FPTO%2Fsrchnum.html&r=1&f=G&l=50&s1=%2220140234968%22.PGNR.&OS=DN/20140234968&RS=DN/20140234968 (last visited Nov. 14, 2014).

2. NT-hPSC through SCNT: This stem cell line is derived from enucleated eggs where patient somatic cell nucleus has been introduced. So, this type of stem cells are histocompatible to the patient in question and may facilitate autologous transplantation with reduced risk of immune rejection. However, this type of stem cell is individual patient-specific and not for a group of patients.[40]

But the fact that egg procurement is integral part of the hpSC research, it requires some ethical issues to be addressed. Women shall be either encouraged to donate the eggs for such researches or egg procurement may open up new commercial avenues. Egg donation is not always harmless for the health of the women. The artificial ovulation may cause some harmful repercussions. There can be short and long-term effects of the procedure of the egg donation. Despite of the ethical dilemma associated to the procurement of good quality eggs, for research or for medically assisted reproduction, egg donation for "monetary consideration" remains in practice. However, United States Patent No. 8,420,393, issued on April 16, 2013 for the "[g]eneration of an autologous stem cell library from human oocytes parthenogenetically activated by high or low oxygen tension", having Elena S. Revazova, Marina V. Pryzhkova, Leonid N. Kuzmichev and Jeffrey D. Janus as the inventors was assigned to the International Stem Cell Corporation (ISCO), California.[41] It seems that for the purpose hSCR, procurement of eggs may become part of the trade. For some critics, the end may not justify the means.

3.1.2.4 ARE THEY SUBSTITUTE OF EACH OTHER OR DIFFERENT FROM EACH OTHER?

The hESC and iPSC have substantial differences. Although they can be merged into same genre of *pluripotency*, they are not same thing from the perspective of means of extraction and safety of application. However, the hESC is believed to hold more potential than the iPSC,[42] whereas autologous iPSCs are believed to be more likely to overcome immune rejection.[43] The human embryonic *pluripotent* stem cells are typically derived from the ICM of the Blastocyst and it is claimed that the derived cells do not possess the capacity to develop into human (Intellepro IP

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[39] *Id.*

[40] *Id.*

[41] United States Patent No. 8,420,393, issued on April 16, 2013. United States Patent and Trademark Office, *USPTO Patent Full-Text and Image Database*, *available at* http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=%2Fnetahtml%2FPTO%2Fsrchnum.htm&r=1&f=G&l=50&s1=8,420,393.PN.&OS=PN/8,420,393&RS=PN/8,420,393 (last visited Nov. 10, 2014).

[42] The hESC is naturally both *pluripotent* and *totipotent.* For the purpose of hESC research, the most conventional derivation involves the extraction of the *pluripotent* cells. The iPSC is induced or reprogrammed to be *pluripotent*. If we consider efficiency in differentiation potential, clearly hESC have upper hand because it is naturally programmed to do so and it may be safer too. The current scientific endeavors related to iPSC basically want to ensure two things:

1. iPSC should have similar differentiation potential and genetic stability as hESC; and
2. When used as therapy, these cells should exhibit satisfactory level of efficacy but not elicit any undesirable immune reactions in the recipient (be it syngeneic or allogeneic iPSC). The autologous iPSC is preferred more than heterologous or allogeneic, as it minimizes many complications (e.g., lack of histocompatibility; the patient derived iPSC should be histocompatible when introduced into the body).

The goal of iPSC is only to produce iPSC, which can be as comparable as possible to the ESC derived from ICM, in terms of differentiation potential and genetic stability.

[43] Each type of *pluripotent* stem cell have its own kind of promises and its unique limitation from the scientific perspective and have different degree of constraint and concern from the conventional ethical perspective.

The patient specific iPSC should theoretically overcome the problem of immune rejection. But it is found in recent studies that some syngeneic tissue derived (syngeneic meaning "from the same host") iPSC did cause immunogenicity in the host (Cao et al. 2014, 1--3). Jiani Cao et al. (2014, 1) commented: "The question whether iPSC derivatives are immnogeneic [immunogenic] or not is straightforward; however, the answer to this question is very complicated due to the developmental randomness of iPSC and the nondeterminacy of the abnormal expression of the minor antigens." The authors concluded that this issue should be taken into serious consideration when implementing iPSC in clinical therapy (Cao et al. 2014).

management: Stem Cells 2014). The cells "derived from fertilized oocytes, and cells of embryo up to about the 8 cell stage" are *totipotent* cells and it is claimed that *totipotent* cells have the capacity to develop as human (Intellepro IP management: Stem Cells 2014). But the extraction process may destroy the developmental potential of the embryo itself, from which the cells are extracted, depending on the extraction technique.[44] The "single-cell biopsy technique" invented and patented by the Advanced Cell Technology (Ocata Therapeutics, Inc.) claimed that their extraction of cells from the "human blastomeres" does not harm the developmental potential of the embryo itself and the derived cells are ESC-like cells (ACT's Blastomere Technology 2014). The iPSCs are also at present believed to be reprogrammed as *pluripotent*.[45] The year 2013 experienced another trial of SCNT technique that cloned human embryo from somatic cell (Tachibana et al. 2013). Are they substitute of each other or different from each other?

However, if differences are to be drawn, some differences do persist among them, if viewed from the source of extraction, safety and efficacy in application. The production cost, e.g., donors sourced or IVF redundant, compensation for donation and the reprogramming costs etc. may also account for the differences. All of these three approaches have the following major concerns:

- For the hESC (derived from the ICM of the Blastocyst), the major concern and challenge would be *ethical consideration regarding embryo destruction*, availability of good quality IVF redundant embryos, the immune compatibility and unknown health effects of the recipients. [46]

- For the embryo cloning through SCNT and hpSC, if the techniques become popular, they may trigger *commercial transaction of human eggs under the plea of egg donation*. The SCNT process requires a steady supply of healthy eggs (often stored as cryopreserved specimen).[47]

- ES Cells from the blastomere cell of the pre-implantation stage embryo derives *tiotipotent* cells (in some instances). The major concern in extraction of blastomere cell from the pre-implantation stage embryo is that this procedure *may compromise* the safety of the "biopsied embryo" / "the resulting child", if it is implanted and may cause unnecessary hindrance in the normal development of the fetus. If PGD is not necessary and this procedure is conducted on the "to be implanted embryo", serious ethical controversies shall arise. [48]

- For the iPSC by direct reprogramming through transcription factors, further intense studies would be required to understand the reprogramming efficiency, cell behavior and genetic

[44] This destruction of the embryo invokes the "exclusion" from the patentability on ethical grounds in many jurisdictions.
[45] The *pluripotency* and the developmental potential of the iPSC had been tested in different animal model systems, except on human.
[46] As the IVF redundant human embryo can be used for research, many countries legitimately do that. But for the effective therapeutic application, healthy eggs, sperms and embryo might be necessary. UK has liberal approach that allows donation of egg, sperm and embryo (HFEA: Donating for Research 2014).
[47] Embryo cloning by SCNT is an invention of 2013 (Tachibana et al. 2013) and no study on efficacy in human for therapeutic purposes are done yet (at the time of this writing). No published reports are available/found on phase I or II clinical trial yet (at the time of this writing).
[48] At present, one of the clinical trials (of ESC derived by blastomere cell extraction) are recruiting patients and research participants in USA "to evaluate the effect of subretinal injection of human embryonic stem cell derived retinal pigment epithelium cells" (ClinicalTrials.gov: Sub-retinal Transplantation of hESC Derived RPE(MA09-hRPE) Cells in Patients With Stargardt's Macular Dystrophy 2014).

stability during and after the reprogramming event, vis-à-vis the immune compatibility and long-term health effect of the recipient. [49]

While the embryo cloning by SCNT directly surfaces concerns over egg donation and women's health, hESC research (by destruction of the embryo) is already prohibited in many countries. Since they are not exactly the same thing, for several reasons, there may be a boost in one type of research technique compared to others. Christoph Bock et al. (2011, 439) published that, "substantial variation has been reported among pluripotent cell lines, which could affect their utility and clinical safety."

Since many researches are now focusing on iPSCs, could that reduce the necessity of hESC research? Scott et al. was of the opinion that, "[i]t is clear that iPSCs are not eclipsing hESCs but have instead emerged as a complimentary technology" (2011, 825). Since a lot of restrictions exist on hESC research, several other techniques of *pluripotent* stem cell researches are on the rise. Numerous research organizations and many literatures insist and advocate that all forms of stem cell research should continue (American Society of Hematology 2013; International Society for Stem Cell Research 2013; Sipp 2011, 275--286) in order to know more about their safety in application, cell behavior in differentiation process, future therapeutic application and further researches beyond. The iPSC should invoke the least objection on ethical grounds; because it is the only technique that is believed to be capable of generating *pluripotent* stem cells without the use and destruction of the *human eggs* and *embryo*. The concern from the bioethical perspectives in general, shall continue to exist for all the emerging techniques of stem cell researches to ensure the human subject protection in biomedical experimentation and the long-term safety of these research outcomes when implemented as therapy.

3.1.2.5 CLINICAL, ETHICAL AND LEGAL CONCERNS OVER THE iPSC

There are certain clinical, ethical and legal concerns that need to be satisfactorily addressed before the iPSC can be considered as ready for the therapeutic purposes:

A. Safety: This is to make sure that "the iPSC derived cells for transplantation" (Requena et al. 2014, 4) are safe to human use and will not induce tumorigenicity and elicit any undesirable immune reaction in the patient's body. This is particularly important from the "long-term malignancy risk" and the "immune rejection" point of view.

B. Efficacy: There is need to prove that iPSC lines generated from different somatic cells are:

(a) fully reprogrammed, because the partially reprogrammed iPSCs have shown limited differentiation capacity in some respect (Zhao 2014, 76);

(b) have minimal or no chance of genetic reversion (to previous somatic cell type from where they have been reprogrammed); and

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[49] First human trial (clinical study/trial on human) of fully reprogrammed iPSC by direct transcription factors began/launched/initiated for age related blindness in August 2013 in Japan (Stem Cells Portal: World's First Induced Pluripotent Stem Cells Clinical Study on Humans Launches in Japan, 2014).

The manufacturing costs can be a concern (Kamao et al. 2014, 215). It is going to be expensive, as there is additional cost of the reprogramming of the somatic cell into the *pluripotent* state like the Embryonic Stem Cells (ESC). Some alternative methods of producing ESC-like cells also show low frequency (Rao 2009, 618--19).

The experiments already done to observe the *pluripotency* and developmental potential of the iPSC are conducted on mouse (Zhao et al. 2010) and non-human primates (Kamao et al. 2014, 205--18).

(c) they behave and function like normal ES cells, i.e., show the *pluripotency* and differentiate to any cell type intended.

Requena et al. (2014, 4) warned that, "[f]urther research is warranted to determine the true long term threat of cancer of iPSC derived cells for transplantation[…]."

C. The "potential to life" issue:

The iPSC, if used as therapy in future, is likely to bypass certain clinical, ethical and legal concerns.

The iPSC generated from the donor somatic cells with matched Human Leukocyte Antigen (HLA) type or the patient's own somatic cell would most likely *minimize or eliminate the possibility of immune rejection* when these cells are used for the treatment purpose. The regenerative potential of human iPSC still needs extensive research and scrutiny (Bock et al. 2011, 439) but definitely holds great promise as future therapy.

The generation of *iPSC will not require fertilized egg*. Nevertheless, they will be fully reprogrammed to retain ESC-like *pluripotency*. In addition, their use will not raise the concern that says that the "developmental potential" of human organism is destroyed, as it is said for the "human embryos."

The ethical debate around the hESC research (derivation from ICM) is that it destroys the "developmental potential" of life as those embryos could grow as human, had they not been destroyed in the research process. They had a "potential to life," if they were implanted into a human uterus. Some advocates find the hESC research as against the core ideas of human dignity. The iPSC is able to circumvent the "developmental potential" of life debate triggered in case of "embryo destruction."[50] But if they (fully reprogrammed iPSC) are injected into the "tetraploid blastocyst" and implanted into the "mouse uterus"[51] (Zhao et al. 2010, 963--71), they show a "potential to life" in a different manner, which might not trigger an ethical objection (if the manner of the therapeutic application is taken into consideration). The human embryo will not achieve its full potential unless it is "implanted" / "placed into a uterine environment" and created the circumstances for the gradual development. But it has the inherent ingredients to be called an *organism* with the developmental potential to become life. Although the techniques of *tetraploid complementation* is viewed as a means to confirm the *pluripotency* of the iPSCs, by employing this assay and by adding the additional step of implantation into the uterus of the recipient mouse, the iPSC satisfies the proposition of "potential to life."

Human embryo as a human organism of earliest stage has the inherent characteristics of "developmental potential", bearing the *prima facie* "potential to life". If it were implanted and allowed to develop inside the human uterus (instead of destroying for the research), it could achieve its "potential to life" gradually and result to live birth. Therefore, human embryo have both "developmental potential" and "potential to life."

The iPSC (reprogrammed through direct transcription factors) is the somatic cell fully reprogrammed to satisfy the *pluripotent* character as that of the hESC. As it is not a human organism of earliest stage, it does not have the inherent "developmental potential". To test the developmental potential, the Tetraploid Complementation (TC) assay would inject the iPSC into the tetrapolid blastocyst. The iPSC itself can not be implanted into the uterus. Only the tetrapolid blastocyst can be implanted into the uterus. If the tetraploid blastocyst is implanted into the human uterus, the iPSC is likely to achieve a "potential to life" gradually and result to live birth (apparently; should there were an

[50] The iPSC is not in itself any organism with inherent capacity to give rise to life. The iPSC is the reprogrammed somatic cells. So their use cannot be considered as the "destruction of life," in a straightforward sense.
[51] Mouse serves as a mammalian (animal) model system.

experiment). Therefore, the iPSC is lacking the "developmental potential", but showing a "potential to life" if the TC is employed.

It is necessary to mention that the tetraploid complementation essay of the fully reprogrammed iPSC has not been tested over human,[52] as a wide ban exists on such experimentation and the "differentiation capacity" of the iPSC is "still limited" (Zhao 2014, 76). It is important to keep in mind that tetraploid complementation is an "assay" to test the *pluripotency* or efficacy of the iPSCs generated. This assay involves a mice based basic mammalian system. The outcome of this assay to confirm *pluripotency* is "potential to live birth," provided that the iPSCs are sufficient enough to give rise to a full term progeny as expected from normal ES cells (Zhao et al. 2010, 963--71). However, this type of assay based on human system to prove the *pluripotency* of human iPSC not only raises ethical concern, it has some peculiarities as well. For tetraploid complementation assay, some special genes are introduced in the iPSC lines in order to make the cells *fluorescent* or different colored from normal embryo. As a result of the color difference, the anatomical parts of the embryo that originated exclusively from the iPSC lines can be easily identified and the *pluripotency* potential of the cell lines can be established. If we try to replicate the same assay in the case of human, it requires implantation of the tetraploid blastocyst into a human uterus to experiment the developmental potential. This essentially means bringing the human embryo to full term and end up making a human baby or an organ with fluorescent color glowing. Therefore, this assay cannot go beyond the "mouse system" due to ethical reasons.

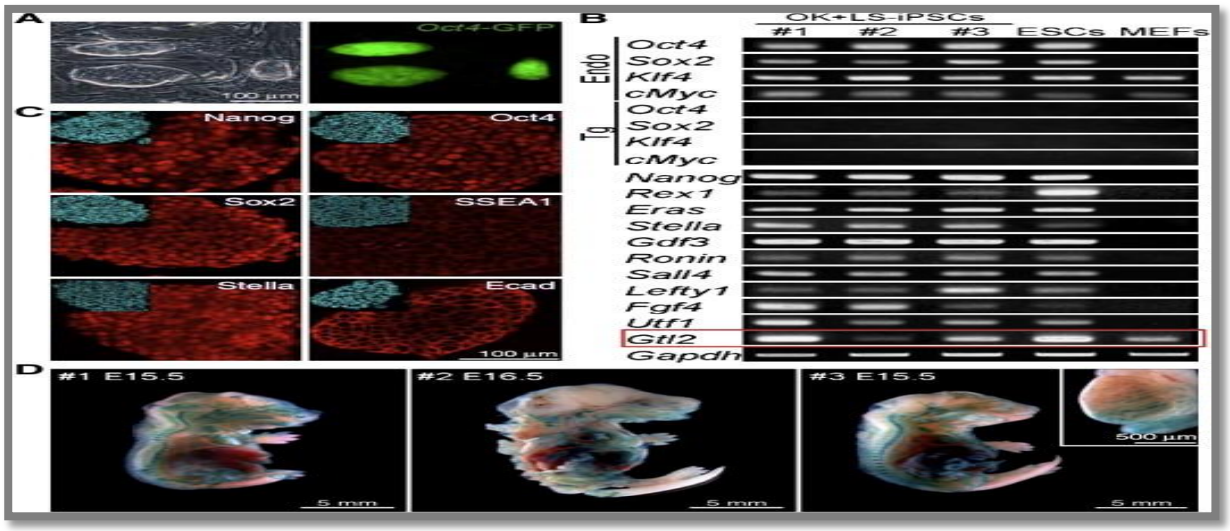

Fig. 3.9 "Pluripotency of induced pluripotent stem cells established by using Oct4, Klf4, and low Sox2 (OK+LS-iPSCs). […]. (D) Contribution of OK+LS- iPSCs derivatives in mouse E15.5 or E16.5 chimeric embryos. The iPSC derivatives were visualized as blue cells by using X-gal staining. […]." (Figure 4, Yamaguchi et al. 2011, 182)

[52] So their *pluripotency* on human is not known.

However, scientists are employing alternative assays to see the developmental potential and *pluripotency* of the iPSCs (Martí et al. 2013, 223--53; Bock et al. 2011, 439--52). The argumentation on *iPSC's potential to life can be viewed as unnecessary*, if the focus can be restrained on procedure that is required for the application only. This *tetraploid complementation* assay is one of the methods used to test the *pluripotency* and the developmental potential of the iPSC; it is not any essential step to the therapeutic application. For the therapeutic application, the iPSC-derived cells require the perfect reprogramming only.

3.1.2.6 HUMAN EMBRYO FOR THE STEM CELL RESEARCH: ETHICAL AND LEGAL DILEMMA

The variations of judgment on ethical grounds are often created by circumstances, background, societal expectation, etc. What is morally wrong in a given context is a difficult question. If the embryo destruction or its particular use is an unethical act or not, that would largely depend on perceptions towards the embryo itself. If someone considers the human embryo as a "life" capable of perceiving humanly attributes and attaches the status of "human being" to an embryo, then the destruction of that embryo could be equated as killing of life according to that person. However, the death of a human is marked by ascribing the status of "deceased" and the expulsion of a fetus is termed as "abortion." The destruction of early embryo is neither of them. Therefore, "destruction" is the mostly used expression for the obliteration of the embryo/pre-embryo for the purpose of scientific experimentation. However, most of the legal texts do not emphasize around the process of "destruction" of embryo, rather they are more focused on the "use" and "commercialization" of that embryo.[53] Noticeable differences exist in the legal and policy framework of the countries around the embryo's use or destruction for the hSCR. The league of people who identifies destruction of embryo as killing of life, presents some arguments and the mostly used one is the "empathy" for the embryo.[54] Whether embryo is biologically equivalent to even an unborn human, or at the early stage of embryogenesis, it is a human biological material, that has to be understood both through and from the scientific and philosophical interpretations. Where scientific explanations have possibility to reduce the multiplicity of opinion, philosophical or ideological convictions can never be unanimous on this issue.

"*When does life begin*" is a common and the most valuable question, answer of which can solve the debate around the status of the embryo. Some strikingly significant events take place during the embryonic development, e.g., fusion of sperm and egg forming the zygote, blastocyst formation, implantation of the blastocyst, formation of the primitive streak, development of early organs, and formation of fetus. The most crucial and intriguing questions may involve at which stage we can say that human life has begun and when the emerging entity would be neurophysically capable of sensing its own existence. Himma (2003, 89-109) rejected the right as "person" of the developing embryo in the first "10 weeks of gestational age" and his reason was that their brain functionality comes into demonstration at or after that period. Condic (2011) while stressing that life of human being commences from the fertilization, i.e., forming the zygote, did not find enough rationale for the other arguments like "viability", "brain maturity" that ascribe human status at certain point of embryonic and fetal development. Antoine Suarez (2011, 190) thought that in order to answer *when life begins*, "one has to take the body exhibiting human architecture and spontaneous movement" into consideration. According to him, "*capability* [italics in the original] for spontaneous movements" at the early stage of development is "the sign for rational ensoulment of a human

[53] For example, Article 6 (2)(c) of the Biotech Directive, 1998 states that, invention will be unpatentable if there is "uses of human embryos for industrial or commercial purposes". Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the Legal Protection of Biotechnological Inventions, 1998 O.J. (L 213), 0013 – 0021, 18.

[54] Deontologists or moral absolutists may find destruction of embryo or its particular use for scientific experimentation in general disturbing.

body" (Suarez 2011, 190). Therefore, in the complex surroundings of differing contrasting opinion, it is hard to suggest an exact *moment* "when life begins" or at which *stage* we can call the growing organism human body and award the status of a human.

Do we need an existing rational human entity to ascribe the status of the "human"? Beyleveld and Brownsword (2001, 115) identified two properties of human, i.e., "consciousness" and "physical embodiment". Ernest Becker (1973, 69) wrote while interpreting Kierkegaard's view on human entity, that human is aware of its "own death and decay". Fertilized human cells while passing through its early embryonic developmental stages (prior to formation of primitive streak), *in vitro* or *in vivo*, would not be able to sense its obliteration. The beginning of the "brain functionality" or the formation of the brain is also a remarkable stage of embryonic and fetal development. There may be connection with the "brain formation" and the determination of the status of the growing organism. We need a legal consensus on the terminologies used in the early stages of the embryonic and fetal development.

Major Key Themes derived from responses to question no. 2[55] shows the perception of the respondents about human embryo, human body and human life:[56]

- The embryo has no rights;
- Embryo at its earliest stage is a mass of undifferentiated cells;
- Presence of "soul" is vital to be considered as human body and human life;
- Embryo has no soul;
- Absence of preciseness, conclusiveness and consensus on the definition of embryo;
- Embryo, human body and human life are integral parts of each other and collectively form a human being;
- Assigning gender to embryo;
- Non-existence of a universality of perceptions;
- "Special respect" for embryo.

The Interpretation of the *Major Key Themes* derived from responses to question no. 2 can be found in Ch. 5.

Major Key Themes derived from responses to question no. 1[57] shows the opinion of the respondents about human stem cell research:[58]

- Against destruction/use of human embryo, other methods are ok;
- Destruction of embryo is "killing";
- Prejudiced about hSCR;
- hSCR is like any other type of scientific research;
- Promising area for therapy;

[55] Question No. 2 was: "How do you perceive the terms 'embryo', 'human body' and 'human life'?".
[56] *Supra* note 18.
[57] Question No. 1 asked: "Do you bear any negative impression / any prejudice about human stem cell research".
[58] *Supra* note 18.

- Somatic/adult stem cell research is acceptable;
- hSCR invokes differing opinions;
- hESC research is politically and ethically controversial.

The respondents expressed different opinions about the use and destruction of human embryo for the hSCR. The Interpretation of the *Major Key Themes* derived from responses to question no. 1 can be found in Ch. 5.

The experts/respondents were asked (question no. 9): "Which application of human embryo can be permitted according to your opinion". The *Major Key Themes* derived from the responses to question no. 9 are the following:[59]

- Use of human embryo for research and innovation in cases of serious disorder;
- "Development of therapeutics" by "Academic/NPO/Government";
- Employing redundant embryos that are anyway destined for destruction;
- Research targeted to find cure or drug development but not through commercial channels;
- Conduct stem cell research by using "cord blood".

The Interpretation of the *Major Key Themes* derived from responses to question no. 9 can be found in ch. 5.

Moreover, the experts were asked (question no. 11) if they "consider that the benefits of hESC (human Embryonic Stem Cell) research is more important than the risks and costs associated to it".

The *Major Key Themes* derived from the responses to question no. 11 focused many scientific issues related to the hESC research:[60]

- Future therapeutic benefits;
- Potential application in personalized medicine and rare diseases;
- Not noticing any risk in research;
- Conducting economic and viability studies;
- Non specialized and *pluripotent* nature of hESC;
- Reducing time and costs of other life science researchers;
- Strict and harmonized regulation;
- Increase of life expectancy;
- Benefit human life, health and the overall society;
- Cord blood is substitute of hESC;

[59] *Supra* note 18.
[60] *Supra* note 18.

- Does not support any kind of stem cell research that involves destroying or putting the human embryo at risk;
- hESC as an applied research employing human embryo without having solid and convincing basic science research data;
- Benefits of hESC are contingent upon costs, affordability, time;
- Each scientific cases vary considerably;
- "Context" and circumstances of each case.

The Interpretation of the *Major Key Themes* derived from responses to question no. 11 can be found in ch. 5.

3.2 HUMAN STEM CELL RESEARCH: LEGAL LANDSCAPE

This sub-chapter explores the legal purview of the hSCR in the countries revisited for the monograph. The comparative discussion is presented in the following tabular form:

Table 3.1 Legal purview of the hSCR in the countries studied

	Research allowed	Research not allowed	Observation
EU policies & European Community Legal Landscape	Research targeted to cure any defect the embryo might have, i.e., research beneficial to the embryo itself is allowed (for the purpose of patentability) by the case of *Oliver Brüstle v. Greenpeace e.V.*, 2011, decided by the CJEU.[61]	Human ESC research by causing the destruction of the embryo is prohibited (for the purpose of patentability) by *Brüstle* case (2011).[62] Article 18 (2) of the Oviedo Convention 1997 prohibits creation of human embryo for research purposes.[63]	Not all European countries have signed and ratified the *Oviedo Convention.* Patent is territorial. Cultural diversity and diverse position on ethical issues of the European States is acknowledged time and again in the European forum and that justifies the diverse goals countries attempt to achieve from science and innovation.
Germany	The German Stem Cell Act of 2002[64] created a	German Embryo Protection Act, 1990	Germany is one of those European

[61] C-34/10, Judgment of the Court (Grand Chamber) 18 Oct. 2011, also *available at* http://curia.europa.eu/juris/liste.jsf?language=en&num=C-34/10 (last visited July 25, 2014).
[62] *Id.*
[63] Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine art. 18(2), Apr. 4, 1997, *available at* http://conventions.coe.int/Treaty/en/Treaties/Html/164.htm (last visited Feb. 12, 2015) [hereinafter Oviedo Convention].
[64] Stammzellgesetz [Stem Cell Act], June 28, 2002 (unofficial translation), secs. 4, 5, 6, (Ger.), *available at* http://www.hinxtongroup.org/docs/Germany1.html (last visited Feb. 13, 2015).

	window of opportunity for doing ESC research under strict conditions and continued the opportunity with the imported embryonic stem cell lines "harvested" before May 1, 2007 ; the "cut-off" date being changed by the amendment of 2008 (from January 1, 2002 (in the original version) to May 1, 2007 (in the amended version)) (Herrmann, Woopen and Brüstle 2008). The Central Ethics Committee for Stem Cell Research (Zentrale Ethik-Kommission für Stammzellenforschung, ZES) is entrusted with the evaluation of the rationale for importation and use of the embryonic stem cell lines in Germany and submits its report to the German federal public health institute RKI which is the licensing authority and also maintains the register of the imported stem cell lines (Robert Koch Institute: Office of the Central Ethics Committee for Stem Cell Research 2014;	(effective from 1991) prevents the creation (fertilization (fusion of of sperm and egg cell)) of embryo *in vitro* for research and experiment (in general; reproductive purpose remain valid exercise);[65] Section 2 of German Embryo Protection Act, 1990 makes "[i]mproper use [according to the text] of human embryos" a punishable act.[66]	countries where "a restrictive but carefully positioned" policy is prevalent for the stem cell research.

[65] Section 1(2) of the Embryo Protection Act 1990 states that, "anyone will be punished who
1. brings about artificially the penetration of a human egg cell by a human sperm cell, or
2. transfers a human sperm cell into a human egg cell artificially, without intending to bring about a pregnancy in the woman from whom the egg cell originated." Gesetz zum Schutz von Embryonen [The Embryo Protection Act], Dec. 13, 1990, Federal Law Gazette (Part I, No. 69, Dec. 19, 1990, Bonn,) at 2746, sec. 2 (Ger.), *available at* http://www.hinxtongroup.org/docs/Germany2.html (last visited Feb. 13, 2015).

[66] Section 2(2) of the Embryo Protection Act 1990 states that, "anyone will be punished who causes a human embryo to develop further outside the body for any purpose other than the bringing about of a pregnancy." *Id.*

	The Robert Koch Institute: Tasks and Aims 2014).		
Italy	Research on embryo is allowed *only if* it is conducted for protecting the health of the embryo itself.[67]	Following researches/activities are not allowed: • creation of embryo for research and experiment;[68] • "interventions cloning through nuclear transfer";[69] and • "embryo splitting".[70]	An environment exists in Italy that may consider destruction of embryo affecting the human dignity and so it is against the constitutional spirit.[71] Article 13 of the Rules on Medically Assisted Procreation 2004, maintains strict restrictions on human embryo related research.[72]
Lithuania	Relating to human embryo, "only clinical observations (non-interventional trials)" are allowed,[73] which is not meant to allow hESC research.	Research using embryo targeting therapeutic application is not possible.[74] Creation of embryo for biomedical research is not allowed.[75] The prohibitive boundary on the human cloning seems to be very expansive.[76] Import and export of embryonic stem cells and embryonic stem cell lines are prohibited.[77]	Embryo cloning through SCNT would attract the wide prohibition.

[67] Norme in materia di procreazione medicalmente assistita [Rules on Medically Assisted Procreation], Legge 19 febbraio 2004, n. 40, in G.U. 24 febbraio 2004, n. 45, art.13(2) (It.).
[68] *Id*. art. 13(3)(a) (It.).
[69] *Id.* art. 13(3)(c) (It.).
[70] *Id.*
[71] Art. 32 Costituzione [Constitution] (It.).
[72] *Supra* note 67, art. 13 (It.).
[73] Law on Ethics of Biomedical Research, Lietuvos Respublikos Seimas [The Seimas of the Republic of Lithuania], 11 May 2000 [As amended upto 15 Nov. 2007 – No X-1325], VIII-1679, art. 3(2) (Lith.).
[74] *Id*.
[75] *Id.*
[76] *Id*. art. 3(4).
[77] *Id*. art. 3(3).

Spain	Until the expiry of the 14th day (after *in vitro* fertilization), the fertilized cells are termed as "pre-embryo" in Spain and they can be used for research and experiment, if donated (created originally for the reproductive purpose but no longer required; can not be created solely for the experiments).[78]	Article 33 of the Law 14/2007 of July 3 on Biomedical Research prohibits creation of embryo solely for the purpose of research and experiment.[79]	Despite the Article 33 of the Law 14/2007 of July 3, 2007 on Biomedical Research prohibited the creation of embryo solely for experiment, Article 15 of the Law 14/2006 of May 26, 2006 allowed the use of those fertilized cells that are redundant or donated from the IVF process for research purposes. Spain maintains difference in using the terminology for human embryo. According to the Spanish legal texts, until 15th day (after fertilization) of the embryonic development, the developing cells are called "pre-embryo," whereas legal texts of other countries like Lithuania address them as embryo.
U.K.	Creation of human embryo *in vitro*, use of embryo for research (for specific purposes) is allowed until the expiry of the 14th day after the fertilization by the Human Fertilisation and Embryology Act 1990, Human Fertilisation and Embryology Act, 2008,	Certain researches using human embryo or creation of embryo *in vitro* shall require license or authorization from the Human Fertilization and Embryology Authority (HFEA), according to the Human Fertilization	

[78] Ley 14/2006, de 26 de mayo, sobre técnicas de reproducción humana asistida [Law 14/2006, of 26 May, on Assisted Human Reproduction Techniques] (B.O.E. 2006, 9292), art. 15 (Spain), *available at* http://www.boe.es/boe/dias/2006/05/27/pdfs/A19947-19956.pdf (last visited Feb. 13, 2015); Ley 14/2007, de 3 de julio, de Investigación biomedical [Law 14/2007, of 3 July, on Biomedical Research] (B.O.E. 2007, 12945), art. 32, 33 (Spain), *available at* http://www.boe.es/boe/dias/2007/07/04/pdfs/A28826-28848.pdf (last visited Feb. 24, 2015);

[79] Ley 14/2007, de 3 de julio, de Investigación biomedical [Law 14/2007, of 3 July, on Biomedical Research] (B.O.E. 2007, 12945), art. 33 (Spain), *available at* http://www.boe.es/boe/dias/2007/07/04/pdfs/A28826-28848.pdf (last visited Feb. 24, 2015).

	and Human Fertilisation and Embryology (Research Purposes) Regulations 2001. [80]	and Embryology Act 1990.[81] After the formation of primitive streak, the research involving human embryo is not allowed.[82]	
US Federal Policy	Stem cell research funding is available for the hESC research. The previously existing barriers were removed in 2009 by the President Barak Obama through an executive order.[83]	Research resulting to human-animal chimera is not eligible for NIH funding. (NIH Stem Cell Information: National Institutes of Health Guidelines on Human Stem Cell Research 2014).	The stem cell research funding for hESC research will be available for the applicants who will use the human embryo created for the IVF purpose and donated by the owner, no longer being required (NIH Stem Cell Information: National Institutes of Health Guidelines on Human Stem Cell Research 2014). The U.S. Food and Drug Administration (FDA) exercises certain authority over the biological products (including stem cell based products) under the Federal Regulations, i.e., "21CFR1271.10"[84]

[80] Human Fertilisation and Embryology Act, (1990) sec. 3(3)(a) (U.K.), *available at* http://www.legislation.gov.uk/ukpga/1990/37/section/3 (last visited Feb. 24, 2015); Human Fertilisation and Embryology Act, (2008) sec. 3(5)(4) (U.K.), *available at* http://www.legislation.gov.uk/ukpga/2008/22/section/3 (last visited Feb. 24, 2015); Human Fertilisation and Embryology (Research Purposes) Regulations, 2001, art. 2(2), *available at* http://www.legislation.gov.uk/uksi/2001/188/pdfs/uksi_20010188_en.pdf (last visited Feb. 24, 2015).

[81] Human Fertilisation and Embryology Act, (1990) sched. 2 (U.K.), *available at* http://www.legislation.gov.uk/ukpga/1990/37/schedule/2 (last visited Feb. 24, 2015);

[82] Human Fertilisation and Embryology Act, (1990) sec. 3(3)(a) (U.K.), *available at* http://www.legislation.gov.uk/ukpga/1990/37/section/3 (last visited Feb. 24, 2015).

[83] Exec. Order 13505, 74 Fed. Reg. 10667, 10667 (Mar. 11, 2009).

[84] 21 C.F.R. §1271.10 (2014).

			and 21CFR1271.15"[85] (Knoepfler 2013, 161--62).
California	California Constitution Article 35, Section 5 allows research with: • Adult stem cells; • Cord blood stem cells; • Pluripotent stem cells (derivation of *pluripotent* stem cells from the IVF redundant embryos and SCNT is allowed). [86]	Human reproductive cloning is prohibited.[87]	The derivation of *pluripotent* stem cells is explicitly legal.
Massachusetts	Chapter 27 of the Act of 2005 on "Enhancing Regenerative Medicine" allows all researches related to stem cells, namely, adult stem cells, cord blood stem cells, SCNT, and "derivation and use of human embryonic stem cells".[88]	Section 8, Chapter 27 of the Act of 2005 on "Enhancing Regenerative Medicine" prohibits reproductive cloning of human.[89]	The law on stem cell research in Massachusetts is very liberal.
New Jersey	Following activities are allowed in the New Jersey: • Adult stem cell research;[90] • [D]erivation and use" of hESC;[91] and	Section 3 of the New Jersey Senate Bill No. 1909 of 2002 prohibited "human cloning".[93]	The laws and policies on stem cell research in New Jersey is liberal.

[85] 21 C.F.R. §1271.15 (2014).
[86] CAL. CONS. CODE art. 35 § 5.
[87] CAL. HEALTH & SAFETY CODE § 24185(a).
[88] 2005 Mass. Act § 1(c).
[89] 2005 Mass. Act § 8.
[90] N.J. Senate Bill 1909 § 2(a) (2002).
[91] *Id.*

	• Somatic Cell Nuclear Transfer.[92]		
South Dakota	It appears that South Dakota favors Adult Stem Cell research (Dakota Voice 2014).	Following medical research that has relevance for the hSCR are prohibited according to the Codified Law of the South Dakota: • Research that would cause destruction of human embryo;[94] • Commercial transaction (sale or transfer) of embryos for non-therapeutic research;[95] and • Human cloning.[96]	South Dakota is one of the most conservative States in hSCR. The definition of "non-therapeutic research" in the South Dakota Codified Laws § 34-14-19 (2013), makes it clear that therapeutic research on the embryo in question for its own benefit is possible, but any type of research that destroys or risks this embryo as a means to develop downstream therapeutic application for the general population is prohibited.[97]
Texas	Several research centers are dedicated to the adult stem cell research, which includes The Texas A&M Health Science Center College of Medicine Institute for Regenerative Medicine (IRM) (Health Science Center: Background 2014) and Texas heart Institute (Texas Heart Institute: Stem Cell Center 2014).		Despite Texas received third largest amount of NIH funding for stem cell research after California and Massachusetts in 2009, the State does not have any policy regulating the Human Stem Cell Research (Matthews and Rowland 2011, 19). However, under the

[93] *Id.* § 3.
[92] *Id.*
[94] S.D. CODIFIED LAWS § 34-14-16 (2013), *available at* http://law.justia.com/codes/south-dakota/2013/title-34/chapter-14/section-34-14-16/ (last visited Dec. 09, 2014).
[95] *Id.* § 34-14-17.
[96] *Id.* § 34-14-27.
[97] *Id.* § 34-14-19.

	The Texas Medical Board's "Practice Guidelines for the Use of Investigational Agents" effective from July 8, 2012 allows the "experimental use of adult stem cells" in patients (Arnold 2012, 1776).[98]		new rules on "Use of Investigational Agents," adopted by the State Medical Board, physicians are allowed to apply experimental therapies and medication, subject to respecting certain safety standards.[99] The physician is playing two roles under this guidelines simultaneously, i.e., "physician-investigators and treating physicians."[100] This is a short-cut that takes the clinical trial from the researcher to the physician directly and apparently at the expense borne by the patients (Arnold 2012, 1776).

3.3 BIOETHICAL CONCERNS IN hSCR

Bioethics as a knowledge discipline combines both theory and practice. It attempts to capture scientific evolution, finds justification in philosophic foundations and reviews the incidents as bioethical discussion from the societal perceptions. Offering encouragement and putting restraint to science, both can be beneficent stand for the bioethics, depending on circumstances. Different thinkers viewed bioethics from different point of views. Jonathan D. Moreno saw bioethics as a *naturalism* (Moreno, 2003, 4) and John Dewey saw it from the lens of *pragmatism* (McGee, 2003, 18). Bethany J. Spielman thinks: "The strands of bioethics are drawn from a variety of sources, methods, theories, and fields, combined in ways that are alternately multidisciplinary, interdisciplinary, and nondisciplinary" (2007, 4). H. Tristram Engelhardt explained that in contemporary bioethics for regenerative medicine there persists disagreement and conflicts between the religious bioethics and secular bioethics (2009, 17--18).

Bioethics is, therefore, as diverse as the human understanding of core ethical behavior. It is most likely that the justification for hESC research can be found in the secular bioethics; rest of the other streams may find it discomforting. The non-compulsory nature of bioethics distinguishes it from legally binding norms. Laws reflective of bioethical principles are emerging in the developed world.

[98] 22 TEX. ADMIN. CODE §198.3 (a) (2012); 37 Tex. Reg. 4929 (July 8, 2012).
[99] 22 TEX. ADMIN. CODE §198.3 (2012); 37 Tex. Reg. 4929 (July 8, 2012).
[100] 22 TEX. ADMIN. CODE §198.3 (a) (2012); 37 Tex. Reg. 4929 (July 8, 2012).

Bioethical principles are enshrined in the international legal instruments both in the form of *soft law* and *hard law*. Several guidelines, non-binding declarations and legal instruments are developed by the non-government organizations, international organizations and inter-governmental organizations.[101] They have contributed to the development of bioethics, gradually towards its formalization.

Following interests are channeled into bioethics:

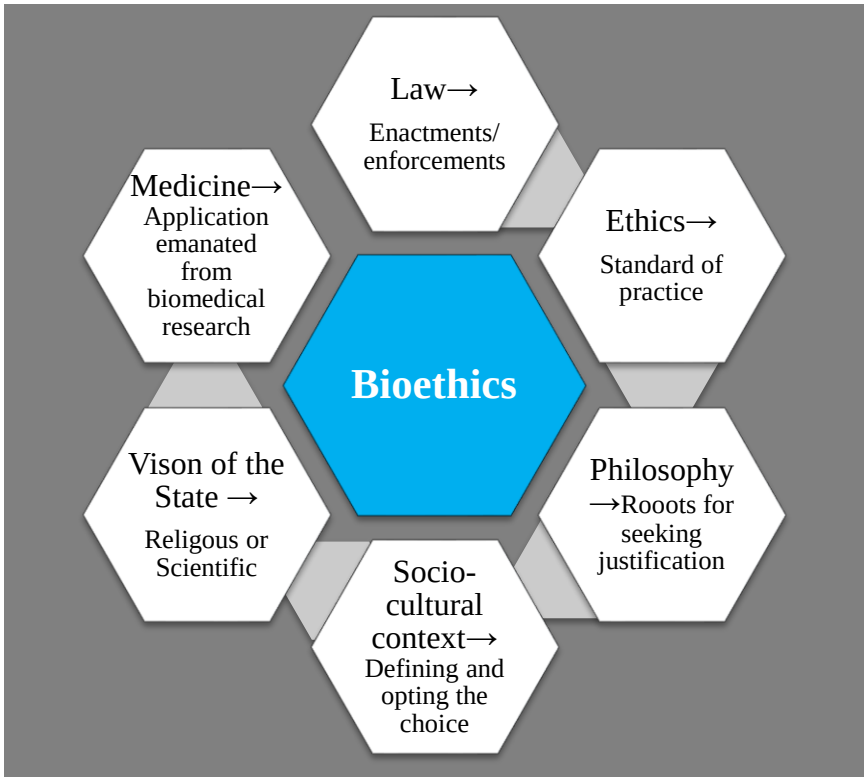

Fig. 3.10 Bioethics' Concerns

There is room to develop a legal instrument for ethical hSCR. It will be difficult to achieve a binding treaty on the subject, as the countries' have different opinions on the purview of the research. The existing bioethics' instruments address the issue either remotely or along with other issues. However, the progress taken place in last two decades towards the ethical biomedical research can be invoked for the hSC research as well.

To develop an efficacious legal framework, the marriage between bioethics and human rights laws can be imagined. Richard E. Ashcroft outlined several advantages of merger between bioethics and human rights norms (2010, 4--9) and stated that, "advantage of linking human rights and bioethics is that the international human rights normative framework interdigitates quite naturally with domestic and international legal systems" (2010, 6). The typical tools that have been developed in the domain of human rights can be used to address the enforcement inadequacies for breach of biomedical research ethics. Countries may also exercise the criminal law and law of tort to regulate biomedical research. The specific laws dedicated to specific area of research may impose penal and tortious obligations. But to redress large scale prolonged breach of ethical norms requiring enforcement of justice between and among several countries may require more than bilateral or transnational treaties.

[101] Such as United Nations (UN), United Nations Educational, Scientific and Cultural Organization (UNESCO), World Health Organization (WHO), Council of Europe (CoE), World Medical Association (WMA), Council for International Organizations of Medical Sciences (CIOMS), International Society for Stem Cell Research (ISSCR), and etc.

Albeit very title, some of the legal instruments demonstrate the already acknowledged interconnectivity between human rights and bioethics.[102] However, bioethical spirits (relevant for public health) can be useful to address the health care inequalities.

I believe that, probably it is high time that bioethics for hSCR reshape itself by taking into consideration:

- the *context* of the application (taking into account the needs and circumstances);
- the *plurality* and *diversity* of the ethical perceptions;
- the *need* of certain degree of *fluidity* to adjust with the ethical conundrum in evolutionary life science.

Arif Jamil (2013a, 41) observed: "It is needless to mention that we are living in an age where our society is more pluralistic than ever[…]. How do we live in harmony with our differences alive? Importance of ethical principles seem to vary according to the context of the individual. […] [T]he number of context increases with the diversity of the individual or groups having differing opinions."

3.3.1 BIOETHICS, INNOVATION AND LAW

In the past, bioethics was more of a merger of ethics and philosophy. As the time goes by, the necessity of transforming the bioethical principles into law is increasing. But it remains a question if the bioethical developments are able to cope with the race of evolutionary developmental biology (Evo-Devo). Between innovation and "legal and ethical response," which one occurs first? The legal and ethical responses are, many a time, subsequent to the innovation. In a race between science, ethics and law, it is the science (innovation) that is ahead in the race, and so, after one race is over, the ethical attention is paid, and thereafter, the need of a legislation is realized. Therefore, bioethics is a subsequent response to the innovation. However, the legal framework can pre-determine the boundary of permissible experiments. In such case, the innovation will never cross the limit foreseeable by law. It is very hard for the legislators to anticipate how idea/experiment (in science) may mould into innovation in future. The effort to foresee "an innovation" and formulate a legal framework compatible to core ethics for that innovation, always will not work, due to the fact that scientific experimentations are capable of demonstrating more creativity than our predictions. In Evo-Devo, we cannot really foresee what is going to be the lab test result of a scientist tomorrow. Therefore, setting a general boundary of norms keeping the core ethics enshrined as a reasonable preemptive action may fall short in a specific situation.

The effort to put general human ethics into binding bioethical legal framework most often fails the test of consensus. The signature and ratification of 1997 Oviedo Convention by a small number of countries' is an attestation of the fact that universal consensus on a legally binding form will be very unlikely. Despite there are universally recognized ethical principles, there will be little consensus when it comes to acknowledge the same ideas into a legally binding treaty.

3.3.2 BIOETHICS AND BIOPOLICY

When bioethics is translated into the biopolicy, it takes a whole new shape and creates different effect. The actors and policy framers utilize their influence during the transformation of theoretical bioethics into law, and hence, defining the purview of the *legitimate research* plays important role (Wolpe and McGee 2003, 181--82). What is permissible research and what should be excluded, is

[102] As for example, the Convention on Human Rights and Biomedicine 1997 and the Universal Declaration on Bioethics and Human Rights, 2005.

always not the ethical concern, rather could be a matter of policy approach. Motives, goals and visions of the actors may play more dominant role in shaping the biopolicy. When those laws and policies are tested in litigations, Courts may play the role of moral arbiter. Despite "bioethics" may be expected to balance science, ethics and law, there is no such expectation from "biopolicy."

3.3.3 ETHICAL hSCR: INFORMED CONSENT, CLINICAL TRIAL, HUMAN SUBJECT PROTECTION AND RESPONDENTS' EXPERIENCE OF CONVENTIONAL MEDICATION FAILURE

WMA Declaration of Helsinki as updated by 64th General Assembly of October 2013 provides guidelines about the gravity of the responsibility of the physician.[103] Article 9 makes it the duty of the physician to protect the human subject taking part in biomedical research.[104] Informed consent is will not be an estoppel for the research subject for invoking the claim of responsibility of the physician; and the burden of proving will lie on the physician that the he has taken best recourses to protect the subject by virtue of this Article 9.[105] This Declaration instructs the physician to abide by the laws of his own country in one hand and international norms, on the other hand.[106] The international norms on biomedical research and on bioethical issues are mostly nonbinding. A very few binding legal texts, such as Oviedo Convention 1997 has been ratified by a small number of countries. If the international norms and principles on the safety standard are nonbinding, it will lack substantial enforcement possibilities. If the State has poor enactments on this or absence of specific policy, then the countries with very low standard of rule of law could be potential breeding ground for human subject abuse in biomedical research. According to Article 37, the physician can apply "unproven intervention" subject to "informed consent from the patient" if he believes that there exists no known cure for the disease.[107] Most of the stem cell based inventions, are at present in the process of invention and unproven to a certain extent about their immediate and long-term consequences. Therefore, the Declaration of Helsinki does not attempt to create an overly ambitions protection regime. Article 30 favors the continuation biomedical research when the subject is not in a state of giving consent.[108] Article 25 to 32 detailed how the informed consent should be obtained.[109] Despite Article 26 mentions that the consent is to be obtained after the subject has understood about the "information",[110] it is hard to be convinced that all biomedical research participants will understand perfectly the intricate biomedical research protocol and terminologies. Therefore, how much understanding is required from the participant and how much information should be provided about the research itself to constitute and satisfy "a fully informed consent" can never be satisfactorily answered.[111]

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[103] WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects, June 1964, *available at* http://www.wma.net/en/30publications/10policies/b3/ (last visited March 12, 2015) [hereinafter Declaration of Helsinki].
[104] *Id.*
[105] *Id.*
[106] *Id.*
[107] Declaration of Helsinki art. 37.
[108] Declaration of Helsinki art. 30.
[109] Declaration of Helsinki.
[110] Declaration of Helsinki art. 26.
[111] HeLa cells, a uniquely surviving cell lines were developed/propagated from the cervix of a cancer patient Henrietta Lacks by Dr. George Otto Gey at Johns Hopkins University (Wikipedia: Henrietta Lacks 2014). The removal of her cells, propagation of the cell lines, biomedical research on them, subsequent application and commercialization were done without her consent and permission (Wikipedia: Henrietta Lacks 2014). She died shortly after the diagnosis but her cell lines continued to be propagated and used for various biomedical research and treatments (Wikipedia: Henrietta Lacks 2014). The biomedical research ethics and codes of ethical practices were not developed during the Henrietta's time (1951). The norms of "informed consent" was not well practiced, but the "The Nuremberg Code" was already in existence which had the first point stating that "[t]he voluntary consent of the human subject is absolutely essential."

Human Rights Guidelines for Pharmaceutical Companies in relation to Access to Medicines annexed to the Report of the Special Rapporteur on the Right of Everyone to the Enjoyment of the Highest Attainable Standard of Physical and Mental Health provided the following instructions in guidelines 21 and 22: **"**A company's clinical trials should observe the highest ethical and human rights standards, including non-discrimination, equality and the requirements of informed consent."[112]

Article 7 of International Covenant on Civil and Political Rights, 1966 provided: "No one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment. In particular, no one shall be subjected without his free consent to medical or scientific experimentation."[113] Article 3(2)(a) of the Charter of Fundamental Rights of the European Union stated: "In the fields of medicine and biology, the following must be respected in particular: […] the free and informed consent of the person concerned, according to the procedures laid down by law". [114] Article 1 of the Oviedo Convention on Human Rights and Biomedicine, 1997 mentioned: "Parties to this Convention shall protect the dignity and identity of all human beings and guarantee everyone, without discrimination, respect for their integrity and other rights and fundamental freedoms with regard to the application of biology and medicine."[115] In the clinical trial, the participants, i.e., patients and healthy volunteers should not be deprived of these rights which are essentially meant to protect their privacy, dignity, and right to withdrawal from the study in the signatory States.

The 10 points of research ethics in doing medical experiments on human subject known as the *Nuremberg Code*[116] has been influential in the formulation of laws relating to biomedical research ethics in the USA, although the code itself has not been directly given into effect. Neil C. Manson and Onora O'Neill (2007, 4) commented: " Informed consent requirements have been extended from research to clinical ethics, and standards for seeking and giving informed consent have been made more explicit and more demanding."

In the United States, the National Research Act of July 12, 1974[117] created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research which navigated to the preparation of *the Belmont Report, 1979*[118] (U.S. Department of Health & Human Services: The Belmont Report 2014). Part B of the Report mentioned "the principles of respect of persons, beneficence and justice" as main principles to be followed in research involving human subject.[119] The Report recognized the autonomy of the individual who is capable of making choice and mentioned the need to protect those who are "immature and incapacitated".[120] The Report emphasized not to cause harm to the subject (as an "obligation"), maximization of benefit and

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(The Nuremberg Code [1947] 1996). But the Nuremberg Code was not given effect into law (The Nuremberg Code [1947] 1996).

Moore v. Regents of the University of California, 51 Cal. 3d 120, 271 Cal. Rptr. 146, 793 P.2d 479, cert. denied 499 U.S. 936 (1991) decided that as the research subject, the patient is entitled to a "full informed consent" which would include information on further economic potentials of the samples extracted from him, but that claim would not extend to a proprietary and property right over the inventions from his cells.

[112] Special Rapporteur on the Right of Everyone to the Enjoyment of the Highest Attainable Standard of Physical and Mental Health, *Interim Rep. on the Right to Health*, U.N. Doc. A/63/263 (Aug. 11, 2008) (by Paul Hunt).

[113] International Covenant on Civil and Political Rights, Dec. 16, 1966, *available at* http://www.ohchr.org/en/professionalinterest/pages/ccpr.aspx (last visited Mar. 13, 2015) [hereinafter ICCPR].

[114] Charter of Fundamental Rights of the European Union art. 1, Mar. 30, 2010, 2010 O.J. (C 83) 389, 392.

[115] Oviedo Convention, *Supra* note 63, art.1.

[116] Published in the *Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10*, Vol. 2, pp. 181-182 (Washington, D.C.: U.S. Government Printing Office, 1949), *available at* http://www.loc.gov/rr/frd/Military_Law/pdf/NT_war-criminals_Vol-II.pdf.

[117] National Research Act of July 12, 1974, Pub. L. No. 93-348.

[118] Published in the Federal Register as a guideline for biomedical research on human subject for the scientists and researchers.

[119] The Belmont Report 1979, *available at* http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html.

[120] *Id.* part B(1).

reduction of risks and harm.[121] The Report thereby set forward the following requirements: (a) standard and fully informed voluntary *consent* obtained in proper fashion; (b) *evaluation* of potential *risks and benefit ratio*; and (c) *justice and fairness* in human *subject selection* for research.[122] The Belmont Report is a good beginning in the American practice of ethical biomedical research on human (as the research subject) and initiated the Federal Regulations' enactment on the subject/discipline. Section 46.117(a) of the Code of Federal Regulations mentioned "the use of a written consent form approved by the IRB[123]and signed by the subject or the subject's legally authorized representative" as the documentation formality of informed consent.[124] Section 1554 of the Patient Protection and Affordable Care Act, 2010 (USA) made the following assurance:

> "Notwithstanding any other provision of this Act, the Secretary of Health and Human Services shall not promulgate any regulation that—
> [….]
>
> (5) violates the principles of informed consent and the ethical standards of health care professionals".[125]

In the United States, within the system of the Office of Food and Drug Administration (FDA) an "Office of Good Clinical Practice" is entrusted with certain responsibilities for human subject protection in clinical trial (About FDA 2014).

[121] *Id.* part B(2).
[122] *Id.* part C.
[123] Institutional Review Boards
[124] 45 CFR § 46.117 (2009), *available at* http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.117.
[125] Patient Protection and Affordable Care Act of 2010, Pub. L. No. 111-148, sec. 1554 (42 U.S.C. 18114) (2010), *available at* http://housedocs.house.gov/energycommerce/ppacacon.pdf.

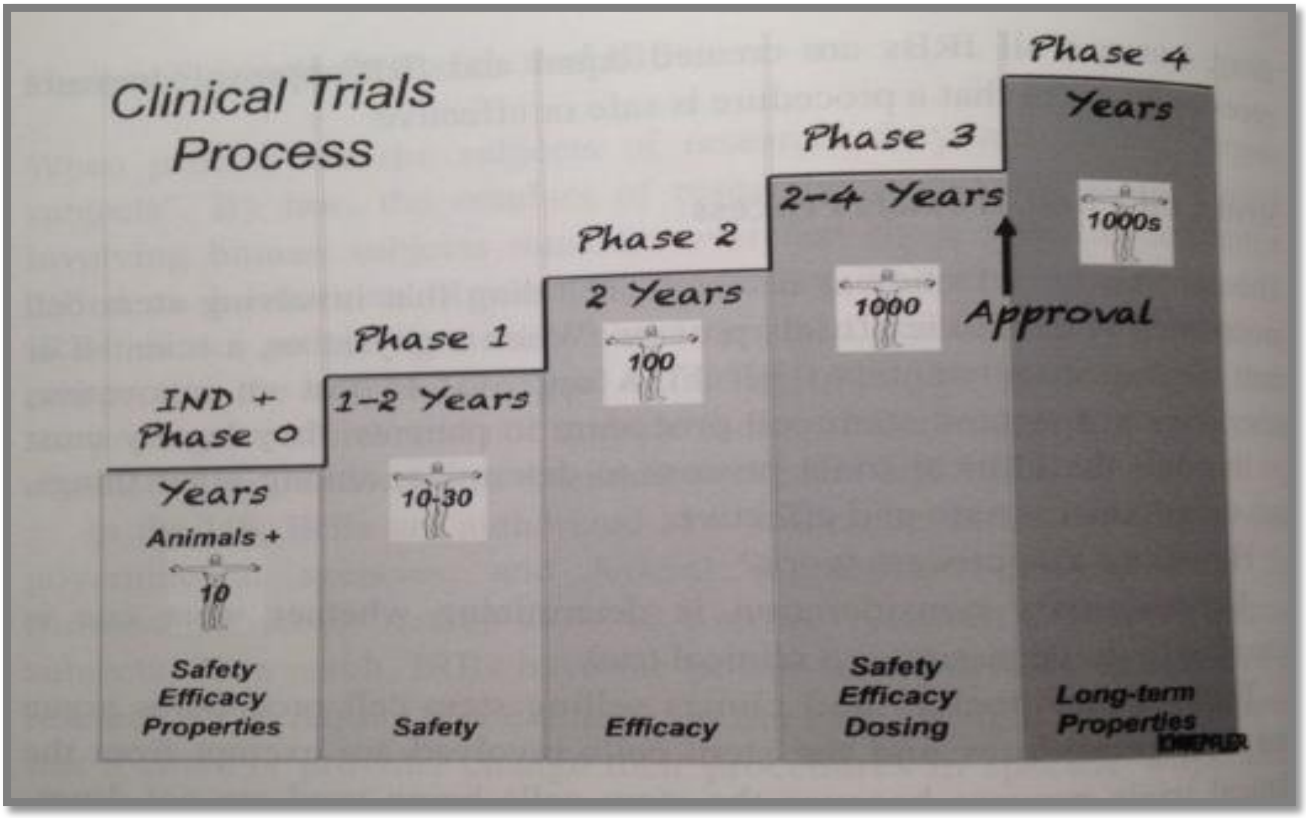

Fig. 3.11 Phase-wise Clinical Trial in the USA (Illustration from Knoepfler 2013, 174). The drawing shows the time required in each phase, number of the research participants and the goal of each phase of the trial (Illustration from Knoepfler 2013, 174)

The World Health Organization offers "International Clinical Trials Registry Platform" that publishes information on clinical trials in a website accessible by all and it offers an opportunity to build an environment of transparency in research involving human subject (World Health Organization: International Clinical Trials Registry Platform (ICTRP) 2014). ClinicalTrials.gov is a database that publishes clinical studies conducted worldwide (190 countries at the time of writing) and in 50 US States (ClinicalTrials.gov Background 2015). Article 40 of the Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on Clinical Trials on Medicinal Products for Human Use, and Repealing Directive 2001/20/EC requires the reporting of all adverse drug reactions (ADRs) to investigational medicinal products through an electronic database "EudraVigilance" maintained by the European Medicines Agency (EMA) in the European Economic Area (EEA).[126]

Therefore, the clinical trial on human need to ensure the following formalities for ethical hSCR:

- Voluntary informed consent by the research participant capable of understanding the procedure and the consequences;
- Right to withdraw from the research;
- Upright position for the human rights and beneficence;
- Well documented procedure, open to the Ethics Committee;
- Accountability to compensate in case of error in conducting the research;
- Post trial care, if there is any likelihood of necessity.

[126] 2014 O.J. (L 158) 1, 36.

With the globalization of biomedical research, poor and developing countries could be lucrative target for clinical trial where informed consent's protocol might not be respected. Aurora Plomer wrote: "An audit of external sponsoring of research in developing countries carried out by the US Food and Drug Administration (FDA) in 2001 showed a steep increase in the number of foreign researchers carrying out research in the decade 1990–2000" (2005, 3). The highest increase was experienced in "Latin America and Eastern European countries" (Plomer 2005, 3). The neighborhood of industrialized and developed countries seems to be the attractive choices for biomedical research and experimentation. However, the victims of many research abuses identified and condemned in the past were chosen from the disadvantaged communities.[127] Marcia Angell (1997, 849) commented: "The fact remains that many studies are done in the Third World that simply could not be done in the countries sponsoring the work. Clinical trials have become a big business, with many of the same imperatives."

The international norm on this subject is still weak for protecting the research participants. In the matters of stem cell based therapy, there is a drive and competition to reach the market faster and ahead of the competitors. As several laboratories in different parts of the world are doing same or similar researches at the same time, the first one gets the patent, in jurisdictions where it is patentable. Therefore, there can be instances where the requirements of the safe biomedical research are not respected.

However, question no. 4 intended to see if the respondents had encountered any situation of conventional medication failure in their life. One might assume that people who had experience of conventional medication failure will have greater tendency of approving the stem cell based therapy as the alternative treatment. In response to the question no. 4 asking if they "have experience of dealing with a situation when conventional medication or treatment could not help", the comments of the respondents highlighted the limitation of the medical science. Following are the *Major Key Themes* derived from responses to question no. 4:[128]

- Admission of the inadequacy of medical treatment;
- Effectiveness of a particular medical treatment can be subjective, due to variability in the biological systems in individuals;
- Medical professionals always encounter the non-efficiency of medical treatment;
- Alternative approaches of treatment may exist;
- Existence of limitation in the conventional approach of treatment taken in the biological science;
- "Metaphysical science" may offer some solutions where "biological science" is ineffective.

The Interpretation of the *Major Key Themes* derived from responses to question no. 4 can be found in ch. 5.

[127] As for example, the victims of Tuskegee Syphilis Experiment were the African Americans who were misinformed about their disease (Angell 1997, 848). They were deliberately let to suffer and die of treatable disease. Many children were born of these victims with congenital syphilis.

[128] *Supra* note 18.

3.4 ACCESS TO THERAPY: COMPULSORY LICENSING, RIGHT TO "HEALTH/HEALTH CARE" AND HEALTH CARE POLICY

The patent has implications for the price of the invented goods. After the expiry of the patent, the *generic* enters the market and the drug price goes down, as the competitors start selling the copy version. The typically used approaches by some of the countries for reducing the cost of the medicine has been issuing the "compulsory licenses to the local manufacturer," allowing "parallel import," and preventing "evergreening of patent". There is very limited leeway to avoid the spirit of the TRIPS Agreement (Chandra 2010, 401), once the country has signed it. The TRIPS spirit is to ensure an effective mechanism for the enforcement of the IPR. The text of the TRIPS does not make reference to the words "compulsory license." It makes reference to the words "licensing contract" to mention the rights of the patent owner.[129] The provisions that would allow the State to make an exception to breach an existing patent are Article 30 and 31, which strongly articulated them as "limited exception" and "other use without authorization";[130] clearly not meant to be read as a compulsory licensing tool for a country to exercise for the *price reduction* purpose.[131] Article 31 makes reference to many requirements, e.g., effort has been made to get authorization, "national emergency", using for limited duration, "public non-commercial use", etc. [132] Some conditions may be relaxed under Article 31(k) for redressing "anti-competitive" effect.[133] But it is not an excuse to loosen the requirement of the TRIPS. However, the Doha Declaration 2001 created an atmosphere for compulsory licensing while acknowledging the right of the States to ensure the "access to medicine" and right to "protect public health".[134] According to paragraph 5(b) of the Doha Declaration, "[e]ach member has the right to grant compulsory licences and the freedom to determine the grounds upon which such licences are granted".[135] Paragraph 5(c) mentioned that interpretation as to determination of circumstances of "national emergency or other circumstances of extreme urgency" shall depend on the member State, while citing "HIV/AIDS, tuberculosis, malaria and other epidemic" as examples of emergency and extreme urgency.[136] In 2006 and 2007, Thailand issued compulsory licences using the TRIPS flexibility combining with the Doha Declaration 2001 for two AIDS drugs (*Efavirenz* and *Kaletra*) and another cardiac drug (*Plavix*), and in consequence of those actions, the "Special 301 Report" of the office of the United States Trade Representative enlisted Thailand in the "Priority Watch List" for disrespecting and weakening patent protection and enforcement and lack of transparency in the application of the compulsory licensing measure (USTR's 2007 Special 301 Report, 27; Macleod 2010, 406--07).

Bringing the stem cell based therapy under compulsory licensing route of TRIPS and Doha Declaration will be difficult. Because the therapeutic application of hSCI will mostly address the degenerative condition of the body, it will not fit into the perceptions of "pandemic" allowing the country to justify the prevalence of urgent needs. Countries are supposed to implement the TRIPS in clear terms of the Agreement. Therefore, compulsory licensing incidents have witnessed objections from the patent owners and the parallel import faces legal obstructions. The rejection of new patent

[129] Agreement on Trade-Related Aspects of Intellectual Property Rights, Apr. 15, 1994, Marrakesh Agreement Establishing the World Trade Organization art. 28(2), Annex 1C, 1869 U.N.T.S. 299, 33 I.L.M. 1197 (1994) [hereinafter TRIPS Agreement].
[130] TRIPS Agreement.
[131] The requirements of allowing the use without authorization of the patent holder is quite strict.
[132] TRIPS Agreement.
[133] TRIPS Agreement.
[134] World Trade Organization, Ministerial Declaration on the TRIPS Agreement and Public Health of 14 November 2001, para. 4, WT/MIN(01)/DEC/2, [hereinafter Doha Declaration], also *available at* http://www.wto.org/english/thewto_e/minist_e/min01_e/mindecl_trips_e.htm.
[135] Doha Declaration para. 5(b).
[136] Doha Declaration para. 5(c).

for the insubstantial contribution over an existing patent, to block the evergreening of patent through the national legislation, are limited to "few countries' instances."

Question no. 12 asked the experts: "Do you think legal obligation for issuing 'licenses on easy terms' or 'compulsory licenses' and 'technology transfer' can bring benefit to the patients by ensuring availability of medication/treatment at a reduced cost and may also serve as incentive for the IPR right owner of human stem cell based inventions/innovations at the same time?". *Major Key Themes* derived from their responses to that question show their diverse thoughts on complex issues of incentive for innovation and fostering access to the therapy:[137]

- Context of the country;
- "Political campaigns";
- "Corruption";
- Excuse to blame the patent for contributing to high costs;
- Does not support mandating or imposing legal obligations on patent holder;
- hSCI / life science inventions should not be IPR protected;
- "Flawed" systems in place.

The Interpretation of the *Major Key Themes* derived from responses to question no. 12 can be found in ch. 5. The experts/respondents emphasized on different issues, e.g., country context, national policy, etc.

The TRIPS Agreement 1994[138] and the TRIPS Plus regime for the IP protection of the pharmaceutical products will contribute to the higher price of the medicines, as believed by many commentators, while shrinking the opportunity of the competition and compulsory licensing (Novogrodsky 2010, 345-346). It often happens that legislations intending to make room for higher and cheaper access to pharmaceutical products get challenged at Court by the Drug companies, e.g., *Pharmaceutical Manufacturers' Association and 41 Others v. President of South Africa and 9 Others* (2001) in which the Medicines Act[139] intended to reduce the prices of the medicine through certain typical approaches like compulsory licensing, parallel import was challenged (Novogrodsky 2010, 349). The Act had triggered the objections from 38 pharmaceutical companies (Elliot et al. 2006, 72). In a tug of war between *human rights instruments*[140]and the *TRIPS Agreement* (enforcing patent rights and IPR (in general protecting inventor's/patentee's interest)), the TRIPS will have advantageous position. Katharine G. Young commented that, "[t]rade rights have stronger enforcement machinery than human rights" (2010, 361). The TRIPS is a legal obligation for the countries to abide by. It is an enforceable legal instrument/tool, maintaining and providing the means of implementation, whereas the human rights' framework comprises mostly of non-bonding soft-law instruments.

[137] *Supra* note 18.
[138] TRIPS Agreement strengthened the patent rights.
[139] Medicines and Related Substances Control Amendment Act, No. 90 of 1997.
[140] They can be invoked to lower prices of therapy, ensure wider access to medicine, protect right to health and safeguard constitutional promise of providing health care.

Identification of health as "right" for the citizens is a recent development. As development taking place in the discipline of human rights and health care, national constitution became one of the major mandates for ensuring the right to health for the subjects.

Time and again, the *right based approach* in access to medicine has taken the forefront of the discussion on health care. Merger of "access to medicine and/or health care" with the notions of human rights recognized in the national context through constitution may make way for higher access to medicine and health care in many countries. This idea may also allow higher access to the stem cell based therapies. Developing new international and national tools are always a challenging task. Recognition of right to health can be found in many international legal instruments. To name a few, there are provisions acknowledging and respecting right to health and access to medicine in:

- WHO Constitution 1946;[141]
- Universal Declaration of Human Rights 1948;[142]
- International Covenant on Economic, Social and Cultural Rights (ICESCR) 1966;[143]
- Declaration of Alma-Ata International Conference on Primary Health Care 1978[144] (Hogerzeil 2006, 371--373), etc.

Invoking and integrating them for ensuring access to stem cell therapy under the broader umbrella of health care would be faster means of capturing the involved agenda in the discussion. However, integrating health care with the human rights and viewing from the right based approach is a relatively new approach and its implications are not much known in the European context. (Herrmann and Toebes, 2011, 420). Right to health can be found to be existing in many legal instruments, but giving recognition to *health care* as right is a difficult stand for the reason that the implementation of such right would require the ability of the State. Hence, for some countries it will be difficult to implement. UN Committee on Economic, Social, and Cultural Rights provided an interpretation of the Article 12 of the International Covenant on Economic, Social, and Cultural

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[141] Preamble to the Constitution of the World Health Organization 1946 provides that, "[g]overnments have a responsibility for the health of their peoples which can be fulfilled only by the provision of adequate health and social measures." Constitution of The World Health Organization, 1946, *available at* http://www.who.int/governance/eb/who_constitution_en.pdf (last visited Mar. 26, 2015).

[142] Article 25 (1) of the Universal Declaration of Human Rights reads as follows:

"Everyone has the right to a standard of living adequate for the health and well-being of himself and of his family, including food, clothing, housing and *medical care* [italics added] and necessary social services, and the right to security in the event of unemployment, sickness, disability, widowhood, old age or other lack of livelihood in circumstances beyond his control." Universal Declaration of Human Rights art. 25, Dec. 10, 1948, *available at* http://www.un.org/en/documents/udhr (last visited Mar. 24, 2015).

[143] Article 12(1) states that, "[t]he States Parties to the present Covenant recognize the right of everyone to the enjoyment of the highest attainable standard of physical and mental health." Article 12(2)(d) incorporated that, the States shall take necessary steps for creating "conditions which would assure to all medical service and medical attention in the event of sickness." International Covenant on Economic, Social, and Cultural Rights art. 12, Dec. 16, 1966, *available at* http://www.ohchr.org/EN/ProfessionalInterest/Pages/CESCR.aspx (last visited Mar. 24, 2015).

[144] The Declaration mentions that, "[t]he Conference strongly reaffirms that health, which is a state of complete physical, mental and social wellbeing, and not merely the absence of disease or infirmity, is a fundamental human right and that the attainment of the highest possible level of health is a most important world-wide social goal whose realization requires the action of many other social and economic sectors in addition to the health sector." It also provides that, "[a]ll governments should formulate national policies, strategies and plans of action to launch and sustain primary health care as part of a comprehensive national health system and in coordination with other sectors." Declaration of Alma-Ata International Conference on Primary Health Care, Sept. 6-12, 1978, *available at* http://www.who.int/publications/almaata_declaration_en.pdf (last visited Mar. 26, 2015).

Rights and it acknowledged in that interpretation that, "[t]he right to health is subject to progressive realisation and resource availability." (Quoted in Backman et al., 2008, 2049).

Right to "health" and right to "health care" may be understood as synonymous expressions but can also be given different meanings, if the realization of the obligation is pursued. Right to "health" can be recognized, but to guarantee the right to "health care" while ensuring the "access" to health care, more capabilities and willingness are required. When *right to health* could be indirectly linked to *right to life* putting the State under obligation to ensure the rights of the individual (Young 2010, 358--59), *right to health care* (if understood differently from the right to health) would be more linked to economic, social and cultural rights getting lesser chance/means of judicial enforcement. However, establishing a direct link between "right to health," "right to health care" and "right to life" would require the enforcement tools, economic capability and legal development nationally and internationally. Therefore, to make sure that stem cell based therapy reaches to the people at reasonable expenses, a lot will depend on:

- the IPR owner;[145]
- the State granting the IP right;
- the type and ability of the health care systems prevalent in that particular State; and
- legal recognition and enforcement tools of right to "health and/or health care."

Article 168(1) (ex Article 152 TEC) of the Treaty on the Functioning of the European Union stated: "A high level of human health protection shall be ensured in the definition and implementation of all Union policies and activities."[146] This implies the commitment of providing high standard of health care, but does not define the set limits. However, Article 35 of the Charter of Fundamental Rights of the European Union asserted that, everyone is entitled to the right to access to preventative health care and "medical treatment" depending on the state's policies.[147] This is a bridge between "right to health" and "right to access the health care" within the European countries.

In the national context, constitutional "recognition and enforcement" of right to "health and/or health care" may help ensuring/fostering the access to stem cell based therapy. Hans V. Hogerzeil and Zafar Mirza found that more than 30 countries did not ratify the ICESCR and right to health is not recognized in more than 60 countries' constitution (2011, 1) and they had the opinion that "inequality" and "discrimination" are the future challenges for accessing the "essential medicine" (2011, 8). There exist huge gaps between affordability of the countries and hence, ability of the States to provide health services varies. Some commentators recommended that pharmaceutical companies need to be brought under responsibility to serve human rights (Hogerzeil and Mirza 2011, 8). Preamble to the Human Rights Guidelines for Pharmaceutical Companies in relation to Access to Medicines provided that, "[p]harmaceutical companies, including innovator, generic and biotechnology companies, have human rights responsibilities in relation to access to medicines."[148]

The report of Paul Hunt[149] on the "Right of Everyone to the Enjoyment of the Highest Attainable Standard of Physical and Mental Health" included following two very significant recommendations in paragraphs 81 and 82 of the report:

[145] I.e., inventor and assignee who had developed the therapy.
[146] Consolidated Version of the Treaty on the Functioning of the European Union, art. 168(1), 2012 O.J. (C 326) 47, 122.
[147] Charter of Fundamental Rights of the European Union art. 35, Mar. 30, 2010, 2010 O.J. (C 83) 389, 398.
[148] Special Rapporteur on the Right of Everyone to the Enjoyment of the Highest Attainable Standard of Physical and Mental Health, *Interim Rep. on the Right to Health*, U.N. Doc. A/63/263, at 15 (Aug. 11, 2008) (by Paul Hunt).
[149] UN Special Rapporteur.

> Several provisions in the TRIPS Agreement, such as article 31 (compulsory licensing), have significant potential for the protection of the public interest in areas bearing upon the right to health. The Special Rapporteur encourages WTO member States to place these provisions in national legislation as a way of safeguarding aspects of the right to health. […]. The Special Rapporteur recommends that States be cautious about enacting "TRIPS plus" legislation without first understanding the impact of such legislation on the protection of human rights, including the right to health. Equally, wealthy countries should not pressure a developing country to implement "TRIPS plus" legislation, unless reliable evidence confirms that such legislation will enhance enjoyment of the right to health in the developing country. [150] (World Health Organization: Reports by the UN Special Rapporteur on the Right of Everyone to the Enjoyment of the Highest Attainable Standard of Physical and Mental Health, with Relevance to Access to Essential Medicines: Intellectual Property and Access to Medicines 2004)

One of the purposes behind supporting the rise of private sector is that it will encourage competition and eventually enhance the quality of service. As the competition can be wiped out by exclusive commercialization through strong IPR and by holding dominant position in the market, there is no question of enhancing quality of service by competition within the term of protection. Hence, the public sector will remain a desired channel of providing the health care services. However, in most cases the patients have the choice to prefer the public or private service provider.

Lostao et al. (2014, 19--25) studied the situation of *access and service* availed by the people in UK and Spain from public and private health care, and found that despite almost everybody have access to public health care, some inclination towards private sector exists, and it exists amongst those who are economically in stronger position. However, their (Lostao et al. 2014) findings also mentioned that "supplementary insurance" that exist alongside the public health care facilities, is mainly to provide those services that are not included in the public service, in the form of higher and more satisfactory services like without wasting time in waiting, dental care, etc. (Lostao et al. 2014, 23--24). Stem cell based therapy can be:

- made available through social insurance or tax based national health system or social security system; and/or
- available, in addition to public health care services, through an additional supplementary insurance, and
- also available through private health insurance and private clinics.

It must be remembered that offering the services simultaneously, may enhance efficiency. But exclusion of the chances of availability from public channels will affect the financially weaker section of the society. Those who do not have employer provided insurance, can not purchase good private insurance package for themselves or do not have substantial means of paying the charges in private hospitals will not be able to avail the advantages of the therapies, in absence of the

[150] Special Rapporteur on the Right of Everyone to the Enjoyment of the Highest Attainable Standard of Physical and Mental Health, *Addendum: Mission to the World Trade Organization*, Doc.E/CN.4/2004/49/Add.1, at 21 (Mar. 1, 2004) (by Paul Hunt).

Government intervention. Therefore, the service delivery through public channels is important not only for ensuring wider access but also to engage the public bodies to innovate means of making the therapies affordable.

Question no. 5[151] explored if the respondents will choose the stem cell based therapy for their dear ones and how they would like to access it. *Major Key Themes* derived from the responses to question no. 5 brought many issues to the fore that link to their choice to accept the therapy and means of accessing the same:[152]

- "Not worried about cost";
- "Decision to accept" the stem cell therapy and the "source" that would meet the expenses of the therapy are separate issues;
- Proof of the efficacy of the treatment;
- State regulation;
- Financed through any source;
- Expects that the costs of the treatment are reasonable;
- Meeting the expense will depend on the particular health care system in a country.

The Interpretation of the *Major Key Themes* derived from responses to Question No. 5 can be found in Ch. 5.

3.4.1 ACCOMPLISHMENTS MADE IN THE COUNTRY CONTEXT

Both the public and private service providers exist in the countries revisited. The social insurance and private insurance also exist at the same time. Consumers of the health care services are free to exercise their choice with respect to receiving their health care service channel. Certain countries have been able to provide adequate service coverage to the citizens through the public channel and public funding and some have not. There are plenty of reasons to believe that the quality of care may vary depending on the affordability of a patient in some countries. It is often true that the private services cost a lot more for the patients.

Despite right to health as can be found in the constitution of some countries, e.g., Italy, Spain and Lithuania, it can not be found as a right guaranteed by the constitution in some others, e.g., UK, USA and Germany. Few countries recognize the access to health care as the right of the citizen and prescribes means to avail it, while making it the duty of the State, e.g. Italy and Lithuania.

Germany

Health Insurance Act 1883 is the foundation of the tradition of social insurance in Germany (German Social Insurance: History 2014). The compulsory Statutory Health Insurance (SHI) gives coverage to

[151] Question No. 5 asked: "Having a choice and at a critical stage of grave illness would you choose stem cell therapy for your family member, if it promises a cure (suppose already available as treatment)?".
[152] *Supra* note 18.

the 90% of the Germans and the people covered are those whose gross income does not exceed 52,200 euros per year (German Social Insurance: Health Insurance 2014; German Health Insurance: Employees 2014). People exceeding that limit may take SHI or opt for private insurance (Worz and Busse 2005, S133) and for both the type of insurances the fund is raised from the employer-employee contributions (German Health insurance: Employees 2014). The additional services that are not covered under SHI, private insurance coverage can be purchased (German Health Insurance: Employees 2014). The SHI Modernization Act 2004 and Health Care Reform Act 2007 were promulgated to bring some improvements in the quality of health care services (Sauerland 2009, 79--98).

Italy

The national health service of Italy was established in the reform of 1978, called *Servizio Sanitario Nazionale* (SSN), is run on tax-payers' money (France, Taroni and Donatini 2005, S187). 97% expenses of public health care met by the general taxes and 15% population having private health insurance are attestation of quite a good picture of health care (France, Taroni and Donatini 2005, S187). The last ranking of the world health systems conducted by WHO was in 2000, and Italy was second best health system after France according to that ranking (Geographic.org 2014). Art. 32 of the Italian Constitution acknowledge health as fundamental right and guarantee the access to health care by the poor/needy individual.[153]

M. Braggion, S. Campostrini and G. Bertin studied data covering the years 2007-2010 from the PASSI,[154] Italian surveillance system for the progress in medical health, and observed that diversity exists in the health care services amongst the twenty-one (21) Italian regions within the country, all of whom enjoying substantial freedom in making policies for themselves within their region (2013, 3). Braggion, Campostrini, and Bertin (2013, 8) reported that, "social determinants can produce (different) inequalities inside different welfare systems."

George France, Francesco Taroni and Andrea Donatini commented after studying Italy's health-care: "Italians are living longer and with fewer functional limitations, but they consistently report low levels of satisfaction with SSN performance. At the same time they express strong support for a universalist, egalitarian and publicly funded health-care system." (2005, S200).

Lithuania

Article 53 of the Constitution of Lithuania guarantees the access to health care and the State undertakes the responsibility of taking care of the health of the subject.[155] The Statutory Health Insurance covers the basic health care expenses for the Lithuanians and the fund for that insurance is raised from general taxes and contribution both (European Association of Hospital Managers: The Lithuanian Health System 2014). The Law on Health System regulates the National Health System of Lithuania (NHSL) and according to Article 11(1) of that law, "individual health care", "public health care", "pharmaceutical activities" are included as concerns of the executive bodies of NHSL.[156] Lithuania depends on both "state budget and health insurance funds" for the health care

[153] Art. 32 Costituzione [Constitution] (It.).
[154] Progressi delle Aziende Sanitarie per la Salute in Italia
[155] Constitution of the Republic of Lithuania, Oct. 25, 1992, *available at* http://www.wipo.int/wipolex/en/text.jsp?file_id=188280.
[156] Law of the Republic of Lithuania Amending the Law on the Health System, Lietuvos Respublikos Seimas [The Seimas of the Republic of Lithuania], Dec. 1, 1998, No.VIII-946 (Lith.).

financing (Merkevicius and Bernotienė 2010, 110). Both the legal system of Germany and Lithuania made the "obligatory health insurance" as compulsory for all (Merkevicius and Bernotienė 2010, 113).

Spain

Sections 43 and 50 of the Spanish Constitution, 1978 recognize right to health, and makes the public bodies responsible to create means to provide access to the health care.[157] Spanish residents, who are employed, students or self-employed can apply for *Tarjata Sanitaria Individual - TSI*, a health card from the Department of Social Security and that will cover most of the expanses of the health care (ExpatFocus: Spain). The additional or the remaining costs of the treatment has to be self-financed or come through private insurance (ExpatFocus: Spain). Only emergency treatment for the holders of TSI social security card or European Health Insurance Cards (EHIC) will be considered for free service in the public hospitals (ExpatFocus: Spain).

The present Spanish health care situation after the recession is not in perfect condition. Reduction in health care budget will delimit many services. The Economist reported that around "873,000 non-registered immigrants" will be excluded from non-emergency health care and the report referred the denial of emergency service to a severely ill tuberculosis patient who died afterwards (The Economist, December 16, 2013). The impact of increased co-payment is excluding pensioners from availing the full course treatment (Quigley et al. 2013, 1977).

United Kingdom

The United Kingdom has "tax based national health system" (Lostao et al. 2014, 19). UK's health care providing structures are mostly financed through sources of public money (Propper 2000, 855), and hence, public structures play wider role. The Department of Health, UK, conducts a programme "Human Rights in Healthcare" which is an affort to highlight health care as basic to perceive several other core human rights (Human Rights in Healthcare 2013). Several UK public bodies, e.g., the Department of Health, British Institute of Human Rights (BIHR), are working together to intertwine human rights and health care (Human Rights in Healthcare 2013). It is mentioned as the duty of the Secretary of State to protect public health under Section 11 of newly framed Health and Social Care Act 2012.[158] The NHS Constitution 2013 outlines one of the seven key principles that guide NHS, which reads as follows: "Access to NHS services is based on clinical need, not an individual's ability to pay" (The NHS Constitution 2013). Goddard and Smith identified various factors that determine if the NHS service would be opted by an individual (2001, 1153). Amongst other reasons/factors that influence the decision of a patient were quality of the service and treatment by the NHS structure, relevant expenses of obtaining the treatment, affordability and opportunity available to the individual from other alternative choices, e.g. insurance, private sources and "community care" (Goddard and Smith 2001, 1153). However, as both public and private health care coexist in the national context of UK, comparatively rich people are the ones who avail the facilities of private health care services, as found in the study by Carol Propper (2000, 873).

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[157] Spanish Constitution [Constitución Española], Dec. 29, 1978 (Spain), *available at* http://www.wipo.int/wipolex/en/text.jsp?file_id=185360 (last visited Feb. 13, 2015).

[158] Health and Social Care Act, (2012), *available at* http://www.legislation.gov.uk/ukpga/2012/7/pdfs/ukpga_20120007_en.pdf.

An individual can complaint to the office of health Ombudsman, if dissatisfied with the services of the NHS or public body providing the health service (Parliamentary and Health Service of Ombudsman 2013). The Care Quality Commission (CQC) in UK looks after the service quality of the health care service providers (Care Quality Commission 2013). The two leading cases, i.e., *R. v. North and East Devon HA Ex p. Coughlan* (1999)[159] and *Grogan v. Bexley NHS Care Trust & Ors* (2006)[160] have extended the responsibility of the NHS and other care providers through its channel to give more specific meaning of the primary health needs.

In the case of *Coombs v. North Dorset NHS PCT* (2013)[161] the Court found that it is possible for the patient to make additional payment for the expenses that are not the statutory responsibility of the NHS (subject to being recommended by the clinician), and there is no bar to make such additional payment in the law and policy.

USA

The Government subsidized insurance for public sector employees, employer provided insurance, privately purchased insurance and privately afforded health care obtained from strong, big and influential private sector are in totality the landscape of American health care. Health care services despite being highly expensive in the USA, the quality of the services and impacts on the human health is not that great, comparing the other nations who are in similar economic conditions (Kalis and Hlafcsakf 2012, 257--58). In this big picture, there is trouble for the uninsured and there is diversity from State to State. The Federal legislations face opposition from the States, from time to time, despite the growing authorities of Federal Laws. In the case of *National Federation of Independent Business, et al. v. Sebelius, Secretary of Health and Human Services, et al*. (2012),[162] twenty-six (26) States opposed the Affordable Care Act 2010, a Federal legislation intending to cover more people under the insurance coverage at a lesser expense.

The Affordable Care Act (ACA), 2010 provided a provision on "Access to Therapies,"[163] but it did not empower an individual in accessing a therapy, rather prescribed which impediments to access to therapy will not be placed in-between the patient and access to the therapy.

Despite ACA is seen by some commentators as a move towards realization of promise of right to health under ICESCR (Battaglia 2012, 155--95), a lot more needed to be done to see health care as a "right" in America. Nicholas A. Battaglia stressed on the necessity of reduction of disparity in the opportunities of health care facilities and the cost of the health care (2012, 170--72,173). It will take some time to see the benefits of the Act, as it is in the progress of creating it effect (Gorin 2011, 83).

It is apparent that the impact of ACA is unclear now. The United States' Supreme Court found the Act in most part valid, as it was challenged by, amongst others, 26 States.[164] However, the Republicans are firmly against this law (The New York Times, June 28, 2012).

Health care services and facilities are not same in all States of the USA. The State of California created a marketplace called *Covered California* (Covered California 2014), to help individual to get insurance, as part of its effort to implement Patient Protection and Affordable Care Act (ACA).

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[159] [2001] Q.B, 213; [2000] 2 W.L.R. 622 CA (Civ Div).
[160] [2006] EWHC 44 (Admin).
[161] EWCA Civ 471, (2013) MHLO 35.
[162] 567 U.S. ___ (2012), 132 S.Ct 2566.
[163] Patient Protection and Affordable Care Act of 2010, Pub. L. No. 111-148, sec. 1554 (42 U.S.C. 18114) (2010), *available at* http://housedocs.house.gov/energycommerce/ppacacon.pdf.
[164] National Federation of Independent Business, et al. v. Sebelius, Secretary of Health and Human Services, et al. 567 U.S. ___ (2012), 132 S.Ct 2566.

California is the first State to start the implementation of the ACA (Covered California 2014), The 10 categories of services provided by the insurance coverage are called “essential health benefits” (Covered California: What does Health Insurance Cover? 2013), and they do not include *regenerative medicine* or does not make direct reference to the stem cell based therapies. Like California, Massachusetts have “state-based marketplace” and implementing the ACA through Medicaid expansion from 2014; New Jersey, South Dakota and Texas have “Federally-facilitated Marketplace” but New Jersey is implementing the ACA from 2014, whereas Texas is not (Kaiser Family Foundation: State Health Facts 2014).

CHAPTER 4
ANALYSIS OF IPR ISSUES

4.1 EVOLVING IPR: WIDENING THE PURVIEW OF PATENT

The patent system since its inception evolved with time. The inclusion of innovations as "patentable invention" continued to happen as we proceeded towards the technologically brighter destiny. Many a times the inclusion as "patentable invention" of new creation or technological contribution was driven by *monetary* and *strategic* purpose, rather than just appreciating and offering the intellectual property protection for the contribution in science. Paul Stark, the Chairman of the National Committee on Plant Patents, also a nursery owner, was the prime figure behind the enactment of Plant Patent Act, 1930 of the USA (Kelves 2002, 4--5).[1] Paul Stark also made contribution in drafting the patent law's bill for that purpose (Kelves 2002, 5). Therefore, it is the "lobbying group" that played a pivotal role for the inclusion of new varieties of plants as patentable invention (Kelves 2002, 4--5).[2] Therefore, apart from guaranteeing and recognizing the rights of the inventor and/or assignee, the patent law has also offered a security for the return of the investment, historically by widening its purview. It is a tool expected to serve the purpose of "incentive for innovation/ invention" through the return of the investment.

4.1.1 LIVING THINGS CAN BE PATENTED

In *Diamond v. Chakrabarty* (1980) the United States Supreme Court held that "live, human-made micro-organism is patentable subject matter under §101".[3] It is the very first case that begun the era of patenting living things in the forms of microorganism. The patent claim of *Chakrabarty* included the *process* of producing a bacteria and the bacteria *itself*.[4] Justice Brennan expressed in dissenting opinion that "it [The Congress] may choose to craft a statute specifically designed for such living things."[5]

The inclusion of the living things (microorganisms) as patentable subject matter was not what the law on patent specifically envisioned; rather the broadness of the provision on "patent scope" offered

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[1] The current version of the 35 U.S. Code § 161 provides the provision of patents for the plants and it states that, "[w]hoever invents or discovers and asexually reproduces any distinct and new variety of plant, including cultivated sports, mutants, hybrids, and newly found seedlings, other than a tuber propagated plant or a plant found in an uncultivated state, may obtain a patent therefor, subject to the conditions and requirements of this title." 35 U.S.C. § 161 (2010).

[2] In the USA, the Plant Variety Protection (PVP) Act enacted in 1970 for the protection of the rights of owners of the sexually reproduced new varieties of plants, was subsequent to the similar enactments emerged in the European continent for the protection of the rights of the plant breeders (Strachan, 1992).

Internationally, for the protection of the rights of the breeders of the new varieties of plants, the International Union for the Protection of New Varieties of Plants (UPOV) emerged under the mandate of the International Convention for the Protection of New Varieties of Plants (UPOV Convention) 1961 (the present version in force is the revised 1991 UPOV Convention).

[3] 447 U. S. 308-318 (1980), also *available at* http://supreme.justia.com/cases/federal/us/447/303/case.html#308 (last visited August 26, 2014).

[4] Diamond v. Chakrabarty 447 U. S. 306 (1980), also *available at* http://supreme.justia.com/cases/federal/us/447/303/case.html#308 (last visited August 26, 2014).

[5] *Id*. at 318.

the opportunity to patent them.[6] After the *Chakrabarty* case,[7] living things (microorganisms) continued to be patented throughout the USA and beyond. The scope of the patent extended over the years from mechanical and chemical inventions to plant protection and other "life forms inventions." The "life science inventions" were also in different times rejected on ethical grounds from patenting in different countries. But a separate uniform international protection framework mandated by a specific legal instrument did not develop to offer the intellectual property protection to those inventions.

4.2 WHAT IS PATENTABLE: LEGAL FRAMEWORK

The patents granted for hSCI can be both for product (e.g., stem cells) and process (e.g., methods of isolation) claims (Overwalle, 2004, 50--51). The legal texts on patenting reveal what are the patentable subject matters and the conditions of patentability. The legal framework for the patent system is multilayered. There are:

- The *international legal framework* comprising of international conventions, international agreements and multilateral treaties,[8] e.g., the Paris Convention for the Protection of Industrial Property (1883), the Patent Cooperation Treaty (PCT) (1970), the Strasbourg Agreement Concerning the International Patent Classification (1971), the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure (1977), the Patent Law Treaty (PLT) 2000, the Agreement on Trade-Related Aspects of Intellectual Property Rights (1994);
- The *regional legal frameworks* created by the multilateral and intergovernmental treaties e.g., European Patent Convention (1973) creating the European Patent organization (EPO) for 38 Countries[9] and the Agreement on a Unified Patent Court (2013) for creating an intergovernmental organization (Patent Court) for EU countries;[10]
- The *regional and supranational legal frameworks*, e.g., the European Union Laws which includes the Treaty on the Functioning of the European Union (TFEU) or EC Treaty (1958), European Patent Convention (1973), Directive on the Enforcement of Intellectual Property Rights (2004), Regulation (EU) No 1257/2012 of the European Parliament and of the Council of 17 December 2012 Implementing Enhanced Cooperation in the Area of the Creation of Unitary Patent Protection, Biotech Directive (Directive 98/44/EC), etc.; and
- National Patent Laws.

Table 4.1 International and European community level legal framework for "patentable invention" and "exclusion" from patenting

	PATENTABLE	EXCLUSION	COMMENTS
TRIPS AGREEMENT	Article 27(1) of the TRIPS Agreement 1994 states that: "patents shall be available for any inventions, whether products or processes, in all fields of technology,	Article 27(2) of the TRIPS Agreement 1994 states: "Members may exclude from patentability inventions, the prevention within their territory of the	Patent is available for "products and processes" and the requirements are typical, i.e., novelty, inventive step and industrial

[6] The inclusion of new subject matter as patentable inventions is also a policy and strategic concern, if viewed from the background of plant patent, where the lobbyist, business groups and stakeholders were the force behind the enactment of Plant Patent Act, 1930 (Kelves 2002, 4--5).
[7] 447 U.S. 303 (1980).
[8] The number of contracting States are different for each of these legal instruments.
[9] All of them are not EU members.
[10] All the EU members are not signatory yet.

	provided that they are new, involve an inventive step and are capable of industrial application."[11]	commercial exploitation of which is necessary to protect *ordre public* or morality, […], provided that such exclusion is not made merely because the exploitation is prohibited by their law."[12]	application. Countries have discretion in exercising the right to exclude inventions from patenting on the grounds of public policy and morality.
EUROPEAN PATENT CONVENTION (EPC)	Article 52(1) of the European Patent Convention, 1973 states: "European patents shall be granted for any inventions, in all fields of technology, provided that they are new, involve an inventive step and are susceptible of industrial application."[13]	According to Article 53(a) of the European Patent Convention, 1973, patents are not available for the "inventions the commercial exploitation of which would be contrary to "ordre public" or morality; such exploitation shall not be deemed to be so contrary merely because it is prohibited by law or regulation in some or all of the Contracting States".[14]	There is no substantial difference in the draft with the TRIPS Agreement, but the *exclusion* on ""ordre public" or morality" has been interpreted and exercised for European Patent (EP) to a greater extent than it is done in other patent systems.
BIOETCH DIRECTIVE	Article 3(1) of the Biotech Directive states: "For the purposes of this Directive, inventions which are new, which involve an inventive step and which are susceptible of industrial application shall be patentable even if they concern a product consisting of or containing biological material or a process by means of which biological material is	Article 6(1) of the Biotech Directive states: "Inventions shall be considered unpatentable where their commercial exploitation would be contrary to *ordre public* or morality; however, exploitation shall not be deemed to be so contrary merely because it is prohibited by law or regulation."[16] Article 6(2)(c) excluded patenting inventions that	What constitutes the "use of human embryos" for the purpose of this Directive? Destruction of embryo only? The provision of the Biotech Directive on exclusion from patenting was interpreted to exclude inventions that

[11] Agreement on Trade-Related Aspects of Intellectual Property Rights, Apr. 15, 1994, Marrakesh Agreement Establishing the World Trade Organization, Annex 1C, 1869 U.N.T.S. 299, 33 I.L.M. 1197 (1994) [hereinafter TRIPS Agreement].
[12] TRIPS Agreement art. 27(2).
[13] European Patent Convention, Oct. 5, 1973 (15th Edition, October 2013), *available at* http://documents.epo.org/projects/babylon/eponet.nsf/0/00E0CD7FD461C0D5C1257C060050C376/$File/EPC_15th_edition_2013.pdf (last visited Feb. 03, 2015).
[14] *Id.*

	produced, processed or used."[15]	"uses […] human embryos for industrial or commercial purposes."[17]	encompasses the *destruction* of human embryos.[18] In a more recent decision of CJEU (2014), hpSC is declared patentable.[19] If the parthenote does not have the capacity to develop to full term, it is not human embryo. [20]

4.2.1 LEGAL FRAMEWORK FOR PATENTING hSCI: GERMANY, ITALY, LITHUANIA, SPAIN AND UK

The following table shows the legal framework at the *national level in Europe* for human stem cell research and patenting (Jamil 2013a, 34--35):[21] The reason for choosing these countries is that their laws and policies on hSCR and patenting of hSCI are diverse.

Table 4.2 The national level legal framework in Europe (from the study context: Germany, Italy, Lithuania, Spain and United Kingdom) for the hSCR and patenting (Illustration from Jamil 2013a, 34--35)

Country	Type of the policy atmosphere prevalant	Laws and policies in force relating to patenting and human stem cell research
Italy	Restrictive Policies Prevalent	1. Constitution of the Italian Republic. Entry into force on 1 January 1948 2. Patent Law (Royal Decree No. 1127 of June 29, 1939, as last amended by Legislative Decree No. 198 of March 19,

[16] Biotech Directive art 6(1), 1998 O.J. (L 213) 0013 – 0021, 18.
[15] Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the Legal Protection of Biotechnological Inventions art 3(1), 1998 O.J. (L 213) 0013 – 0021, 18) [hereinafter Biotech Directive].
[17] Biotech Directive art 6(2)(c), 1998 O.J. (L 213) 0013 – 0021, 18.
[18] See ch. 4.2.3 EXCLUSION FROM PATENTABLE INVENTIONS: COUNTRY EXAMPLES.
[19] Case C‑364/13, International Stem Cell Corporation v. Comptroller General of Patents, Designs and Trade Marks, Judgment of the Court (Grand Chamber) 18 Dec. 2014, also *available at* http://curia.europa.eu/juris/document/document.jsf;jsessionid=9ea7d0f130de9c4121923b8f43769c42c1706a04f989.e34KaxiLc3eQc40LaxqMbN4ObheSe0?text=&docid=160936&pageIndex=0&doclang=EN&mode=lst&dir=&occ=first&part=1&cid=88991#Footnote* (last visited Dec. 22, 2014).
[20] The CJEU held: "Article 6(2)(c) of Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions must be interpreted as meaning that an unfertilised human ovum whose division and further development have been stimulated by parthenogenesis does not constitute a 'human embryo', within the meaning of that provision, if, in the light of current scientific knowledge, it does not, in itself, have the inherent capacity of developing into a human being, this being a matter for the national court to determine." *Id.* paragraph 39.
[21] The content of this table appeared in the article of Arif Jamil published in the ""Social technologies'13 conference proceedings", ISBN 978-9955-19-586-3 (online)" (Jamil 2013a, 34--35).

		1996) 3. Law No. 78 of 22 February 2006 Enacting the EU Directive 98/44/EC in Italy 4. Law No. 40, Regulation of Medically Assisted Reproduction (2004)
Lithuania	Restrictive Policies Prevalent	1. Law on Patents, 18 January 1994, No. I-372 (As amended upto 10 May 2007) 2. Law on Ethics of Biomedical Research 2000, as amended upto 2007 3. Oviedo Convention on Human Rights and Biomedicine (2002)
Germany	Restrictive but carefully positioned policies prevalent	1. Patent Law (enacted on 5 May, 1936, as amended upto 31 July, 2009) 2. Embryo Protection Act (1990) 3. Stem Cell Act 2002 and amendment of 2008 (Law on Protection of Embryos in Connection with Importation and use of Human Embryonic Stem Cells) 4. Act of Quality and Security of Human Tissue and Cells (2007) 5. Medicinal Products Act, 2009
Spain	Not so restrictive but carefully positioned policies prevalent	1. Law on Patents, No. 11/1986 (enacted 20 March, 1986, entry into force 26 June, 1986) 2. Law on Assisted Human Reproduction Procedures. Law No. 14/2006 of 26 May 2006 3. Law on Biomedical Research, Law No. 14/2007, of 3 July 4. Oviedo Convention on Human Rights and Biomedicine (Entry into force in Spain from 2000) 5. Additional Protocol to the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine, on the Prohibition of Cloning Human Beings (Entry into force in Spain 2001)
United Kingdom	Not restrictive at all, rather liberal policies prevalent	1. The Patents Act 1977, Enacted 29 July, 1977 2. Human Fertilisation and Embryology Act (1990), as amended by the Human Fertilisation and Embryology Act 2008 3. Human Reproductive Cloning Act (2001) 4. Human Fertilisation and Embryology Act 2008

4.2.2 IN THE USA

Which inventions are patentable and who may obtain a patent is described in 35 U.S. Code § 101 in the following language: “Whoever invents or discovers any new and useful process, machine,

manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title."[22] According to the 35 U.S. Code, "[t]he term "invention" means invention or discovery"[23] and "[t]he term "process" means process, art or method, and includes a new use of a known process, machine, manufacture, composition of matter, or material."[24] What was patentable invention according to the Patent Law of 1793 is that, "any new and useful art, machine, manufacture, or composition of matter, or any new or useful improvement thereof." (Quoted in Kevles 2002, 1). The difference with the previous original version and the present version is that, now the word "process" is substituted for the word "art." Therefore, for the purpose of patenting in the United States, the literal meaning of the text suggest that patentable inventions also include the "discovery" and "process."

A good number of laws relevant for the patent, hSCR and hSCI are in force in the USA. Appendix 1 "THE LEGAL FRAMEWORK" of this monograph provides a list of the Federal legislations and the State laws existing in the USA.

4.2.3 EXCLUSION FROM PATENTABLE INVENTIONS: COUNTRY EXAMPLES

According to Article 6 of the Biotech Directive, inventions that use the human embryo for "industrial or commercial purposes" are excluded from patentability, as their commercial exploitations would be contrary to "ordre public or morality".[25] According to the Article 53(a) of the European Patent Convention, if the "commercial exploitation" of the invention is "contrary to "ordre public" or morality", it is excluded from patenting.[26] *Oliver Brüstle v. Greenpeace e.V.*[27] is an application of the above provisions towards the widening of the exclusion from patenting. Paragraph 53(3) of the Judgment of the Court (Grand Chamber) excluded inventions in the following words: "Article 6(2)(c) of Directive 98/44 excludes an invention from patentability where the technical teaching which is the subject-matter of the patent application requires the prior *destruction of human embryos* or their *use as base material*, whatever the stage at which that takes place and even if the description of the technical teaching claimed does not refer to the use of human embryos."[28][Italics added]. Paragraph 53(2) of the Judgment of the Court (Grand Chamber) stated the extent of the exclusion in the following words: "The exclusion from patentability concerning the use of human embryos for industrial or commercial purposes set out in Article 6(2)(c) of Directive 98/44 also covers the use of human embryos for purposes of *scientific research*, only use for therapeutic or diagnostic purposes which is applied to the human embryo and is useful to it being patentable."[29][Italics added]. Therefore, the research that destroys human embryos will not be able to get a patent (European Patent) if it results to an invention. The only invention that remains patentable is the one that uses the human embryo for the therapeutic purposes and is useful to the embryo itself.

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[22] 35 U.S.C § 101 (2011).
[23] 35 U.S.C. 100(a) (2011).
[24] 35 U.S.C. § 100(b) (2011).
[25] Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the Legal Protection of Biotechnological Inventions, 1998 O.J. (L 213) 0013 - 0021.

It is worth mentioning that therapeutic application of "any invention that has been patented," will be subject to commercial exploitation automatically. Therefore, if "therapeutic application" is the only purpose the invention is expected to serve, and if "commercial exploitation" has to be separated from it, the invention can not be patented. Because patent is a tool for commercial exploitation *per se*.

[26] European Patent Convention, Oct. 5, 1973, 13 I.L.M. 268, *available at* http://www.epo.org/law-practice/legal-texts/html/epc/2013/e/ar53.html (last visited Dec. 09, 2014).
[27] C-34/10, Judgment of the Court (Grand Chamber) 18 Oct. 2011, *available at* http://curia.europa.eu/juris/liste.jsf?language=en&num=C-34/10 (last visited July 25, 2014).
[28] Oliver Brüstle v. Greenpeace e.V, *supra* note *27*.
[29] *Id.*

Table 4.3 Exclusion from "patentable inventions"

Country	Exclusion from Patentability	Comments
Germany	Following are excluded from patenting: • Human cloning; [30] and • Inventions that use "human embryos for industrial or commercial purposes."[31]	What constitutes "use of human embryos" for the purpose of this Act? Destruction of embryo? Extraction of blastomere cell from the pre-implantation stage embryo?
Italy	Art. 13 provides that the "[i]nventions the working of which would be contrary to public order or morality may not form the subject matter of a patent".[32]	No direct reference of hSCI are found in the excluded inventions.
Lithuania	Following are excluded from patenting: • Human cloning;[33] • Inventions that use "human embryos for industrial or commercial purposes";[34] • "inventions the commercial exploitation of which would be contrary to public interests, principles of morality and humanity."[35]	What constitutes "use of human embryos" for the purpose of this Act? Destruction of embryo? Extraction of blastomere cell from the pre-implantation stage embryo? Inclusion of the ideas of "principles of morality and humanity,"[36] in the patent law is a new approach that acknowledge the link between patent and humanitarian needs.
Spain	Likely to be excluded: • "inventions whose publication or working	There is no strong exclusion provision observed in the patent law.

[30] Patent Act (as amended by the Law of July 31, 2009) Section 2(2)(1), *available at* http://www.wipo.int/wipolex/en/text.jsp?file_id=238776 (last visited Jan. 28, 2015).
[31] *Id.* sec. 2(2)(3).
[32] Patent Law (Royal Decree No. 1127 of June 29, 1939, as last amended by Legislative Decree No. 198 of March 19, 1996), *available at* http://www.wipo.int/wipolex/en/text.jsp?file_id=128268 (last visited Jan. 28, 2015).
[33] Law on Patents of 18 January 1994, No. I-372 (As last amended on 10 May 2007 – by Law No. X-1119) Article 2(1), *available at* http://www.wipo.int/wipolex/en/text.jsp?file_id=188691 (last visited Jan. 28, 2015).
[34] *Id.* art. 2(3).
[35] *Id.* art. 2(3).
[36] *Id.* art. 2(3).

	would be contrary to public order or morality."[37]	
U.K.	A general exclusion states: "A patent shall not be granted for an invention the commercial exploitation of which would be contrary to public policy or morality."[38]	There is no strong exclusion provision observed in the patent law.
U.S.A.		There is no exclusion on "*ordre publi*c and/or morality" in the US patent law. There is no exclusion from patenting for the "use and destruction" of the human embryo.

4.2.3.1 THE EXTENT OF UNIVERSAL EXCLUSION FROM PATENTING hESC BASED INVENTION

Patenting hESC based inventions attract most of the ethical controversies. Is hESC based invention universally excluded from patenting? The answer is "no." Is it possible to patent all kinds of stem cell based inventions in those countries that do not exercise wider exclusion from patentability? The answer is "yes."

It is necessary to see how the international depositary institution for the purpose of deposit of microorganisms for patent protection under the Budapest Treaty, 1977 perceives the ethical requirements. Although they are not the patent granting authority, they preserve the specimen of the patented invention. Despite patent protection on hESC based invention has legal constraint in Europe, it does not have the international constraint. The National Institute for Biological Standards and Control (NIBSC) of UK is the International Depositary Authority under the Article 6(2) of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure, 1977 (World Intellectual Property Organization: Budapest Notification No. 227 2014). Since 2002, the NIBSC is hosting the UK Stem Cell Bank which is the repository for all kinds of stem cell lines including hESC (World Intellectual Property Organization: Budapest Notification No. 227 2014). UK Stem Cell Bank will accept the deposit of the stem cell lines and shall also provide stem cell lines "both for basic research and for the development of clinical applications" (World Intellectual Property Organization: Budapest Notification No. 227 2014).

The National Institute for Biological Standards and Control (NIBSC) of UK shall accept as depository for the purpose of patent protection all "[h]uman cell lines (including embryonic and somatic stem cell lines)" (National Institute for Biological Standards and Control (NIBSC): NIBSC Guide to the Deposit of Cultures for Patent Purposes 2014). The NIBSC Guide to the Deposit of Cultures for Patent Purposes clearly mentioned that "NIBSC reserves the right to refuse deposits which in its opinion represent unacceptable hazards, significant technical or other difficulties, or where ethical considerations are inconsistent with those applied in the UK." (National Institute for Biological Standards and Control (NIBSC): NIBSC Guide to the Deposit of Cultures for patent

[37] Law No. 11/1986 of March 20, 1986 on Patents Section 5(1)(a), *available at* http://www.wipo.int/wipolex/en/text.jsp?file_id=126574 (last visited Jan. 28, 2015).

[38] The Patents Act 1977 (Chapter 37, as amended by the Tribunals, Courts and Enforcement Act 2007) Section 1(3), *available at* http://www.wipo.int/wipolex/en/text.jsp?file_id=330537 (last visited Jan. 28, 2015).

Purposes 2014). Hence, the ethical standards for deposit of stem cell lines for the purpose of patent protection under the Budapest Treaty, 1977 is the standard that is prevalent in the UK. It appears that the emphasis for this purpose in the UK's policy is that "the cell line(s) has been ethically sourced with fully informed and free donor consent" (National Institute for Biological Standards and Control (NIBSC): Patent Depositary Service 2014). It is a universally acknowledged requirement that informed consent was obtained from the donors. Therefore, the ethical standard is the liberal, general and universal standard. Hence, there is no ethical barrier causing universal exclusion from patenting hESC based invention. There is no universal or international patent either.

However, there can be a long discussion if the inclusion of stem cells for the deposit under the Budapest Treaty 1977 is an ideal thing, while associating/treating them with/as "microorganism." I asked Tania S. Bonny, Researcher of Public Health at the University of Florida, USA, about the differences of microorganisms and stem cells and the suitability of deposit of human stem cells under the Budapest Treaty, 1977 for the purpose of patent protection. In her opinion:

> Microorganisms and stem cells are not the same things in the strict sense but they both can be considered as "living forms." Stem cells in nature are not discreet entities rather they are part of larger living form, e.g. animal, human. Microorganisms can live freely in soil, air, water or remain associated with other non-living or living forms. But usually they are not essential for viability of a larger living form. Microbes are usually dispensable whereas stem cells are indispensable for higher multicellular organisms. For example, a mammal or human body cannot develop or remain viable without the stem cells that give rise to different cell types of the body. The Budapest Treaty, 1977 does not define the term "microorganism." It seems that the Treaty identifies microorganism from the context of "genetic stability" and "issue of reproducibility." The Treaty seems to consider bacteria, virus, fungi and all types of cell lines (which include stem cells) etc. collectively as "microorganisms." The justification can be that they are all living forms and possess DNA/RNA as their genetic material. They are all, therefore, susceptible to small and large scale genetic mutations and once mutated they might or might not possess the desired features anymore. Some mutations occur by chance and may impart a quality in the organism accidentally. Spontaneous (chance) mutations by various known and unknown mechanisms are frequently observed in natural and laboratory settings. Yet some mutations are introduced by the scientists deliberately to impart a desirable characteristic. Thus scientists need to confirm the genetic stability of the life form on which the invention is based upon. Invention borne out of a "chance mutation" which cannot be reproduced is not patentable. (Tania S. Bonny, in email with the researcher, July 24, 2014)

Therefore, the deposit is an action which satisfies the adequacy of the *disclosure* for the purpose of the patent protection. While the "written description" might not always be the perfect description of the invention, a deposit may strengthen the IP protection.

4.3 PATENTABILITY REQUIREMENT FOR THE hSCI

The standard requirements for patentability are:

- Novelty (Newness);

- Inventive step (Non-obviousness);[39] and
- Industrial application (Utility).

Does a hSCI satisfy these requirements? What are the uncertainties, ambiguities and possibilities surrounding the hSCI when they are tested for each of these requirements?

4.3.1 NOVELTY IN hSCI

If the "invention makes a technical contribution to the state of the art" (MacQueen et al. [2008] 2010, 512--13), it is a patentable invention and may satisfy the requirement of novelty. Many of the methods of derivation of hSCs are new/novel, e.g., the reprogramming of iPSC by the *direct introduction of transcription factors* by Takahashi et al. (2007), *modified* SCNT protocol by Tachibana et al. (2013), etc. Article 5(2) of the Biotech Directive 1998 states that, "[a]n element isolated from the human body or otherwise produced by means of a technical process, including the sequence or partial sequence of a gene, may constitute a patentable invention, even if the structure of that element is identical to that of a natural element."[40] The clause saying "element isolated from the human body or otherwise produced by means of a technical process"[41] can be applied in case of derivation of hESC, SCNT (NT-ESC) and iPSC technologies in different ways. Use of caffeine, the protein phosphatase inhibitor by the team of Mitalipov (Tachibana et al. 2013, 1231) demonstrates the application of "technical process"[42] and an evidence of a *modified protocol* for embryo cloning by SCNT. The *direct reprogramming* of somatic cells into iPSC by *transcription factors* (Takahashi et al. 2007) can also be expressed in other words as produced "by means of a technical process".[43]

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[39] The term "inventive step" is commonly used in Europe and the term "non-obviousness" is used in the USA for the same expression.
[40] Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the Legal Protection of Biotechnological Inventions, 1998 O.J. (L 213), 0013 – 0021.
[41] *Id.* art. 5(2).
[42] *Id.*
[43] *Id.*

Patents on iPSC technology is increasing day by day, ever since it started and some of the patents at the pioneering stages are:

- EP 1970446, date of publication August 3, 2011 having Shinya Yamanaka as the inventor and Kyoto University, Kyoto, Japan as the assignee for the "[n]uclear reprogramming factor". European Patent Office, *Espacenet Patent search*, *available at* http://worldwide.espacenet.com/publicationDetails/originalDocument?CC=EP&NR=1970446B1&KC=B1&locale=en_EP&date=&FT=D (last visited Nov. 5, 2014);
- United States Patent No. 8,048,999, issued on November 1, 2011 having Shinya Yamanaka, Kazutoshi Takahashi and Keisuke Okita as the inventors and the Kyoto University, Japan as the assignee for the "[n]uclear reprogramming factor". United States Patent and Trademark Office, *USPTO Patent Full-Text and Image Database*, *available at* http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO2&Sect2=HITOFF&p=1&u=%2Fnetahtml%2FPTO%2Fsearch-bool.html&r=12&f=G&l=50&co1=AND&d=PTXT&s1=8,048,999&OS=8,048,999&RS=8,048,999 (last visited Nov. 5, 2014);
- United States Patent No. 8,058,065, issued on November 15, 2011, having Shinya Yamanaka and Kazutoshi Takahashi as the inventors and Kyoto University, Japan as the assignee for the methods of generating iPSC by the nuclear reprogramming factor "Oct3/4, Klf4, c-Myc and Sox2". United States Patent and Trademark Office, *USPTO Patent Full-Text and Image Database*, *available at* http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO2&Sect2=HITOFF&p=1&u=%2Fnetahtml%2FPTO%2Fsearch-bool.html&r=8&f=G&l=50&co1=AND&d=PTXT&s1=8,058,065&OS=8,058,065&RS=8,058,065 (last visited Nov. 5, 2014);
- United States Patent No. 8,129,187, issued on March 6, 2012, having Shinya Yamanaka, Kazutoshi Takahashi and Keisuke Okita as the inventors and the Kyoto University, Japan as the assignee for the "[s]omatic cell reprogramming by retroviral vectors". United States Patent and Trademark Office, *USPTO Patent Full-Text and Image Database*, *available at* http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO2&Sect2=HITOFF&p=1&u=%2Fnetahtml%2FPTO%2Fsearch-

The hESC based inventions may also encompass the "isolation" and "technical process".[44] Huan Zhu (2011, 225) wrote: "hESCs isolated from embryos and cultured in specific media are novel because after being cultured in an artificial environment, the molecular structure, characteristics and even chromosomal structure may be changed and differ from the cells of the embryos from which they were derived." However, "newness" and "novelty" have different meaning for the purpose of satisfying the requirement of patentability in the United States. Therefore, "invention in ordinary sense" and "patentable inventions" are two different things. The requirement for patentability in the 35 U.S. Code § 102[45] indicates that the invention has to be not only "new" but also "novel", meaning that it is not defeated by any disclosure or prior art (Palombi 2009, 222).

However, Article 5(1) of the Biotech Directive 1998 states that, "[t]he human body, at the various stages of its formation and development, and the simple discovery of one of its elements, including the sequence or partial sequence of a gene, cannot constitute patentable inventions."[46] The exclusion of hESC inventions (encompassing the *destruction* of human embryo) from patenting in Europe is based on the interpretation of Article 6(2)(c) of the Biotech Directive. The CJEU in the case of *Oliver Brüstle v. Greenpeace e.V.*, 2011[47] found the commercial exploitation of inventions encompassing the destruction of the human embryo as against the spirit of the "*ordre public* or morality".[48] In the United States, the scenario is different from the European supra national legal framework. In the US, patenting enjoys wider freedom and hESC related inventions can be patented.

4.3.2 INVENTIVE STEP/NON-OBVIOUSNESS

Substantial effort, research and study through trial and error is required for making the claim that the reprogrammed cells will function towards the desired application. Non-obviousness to a person skilled in art can be established and the human contribution for the "inventive step" may justify an IP protection.[49] The non-obviousness requirement is laid down in 35 U.S. Code § 103 as following:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains.[50]

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bool.html&r=2&f=G&l=50&co1=AND&d=PTXT&s1=%22US+8129187%22&OS=%22US+8129187%22&RS=%22US+8129187%22 (last visited Nov. 5, 2014).

[44] *Supra* note 40, art. 5(2).
[45] 35 U.S. Code § 102 (a) states that, "[a] person shall be entitled to a patent unless—
(1) the claimed invention was patented, described in a printed publication, or in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention". 35 U.S.C. § 102 (2013).
[46] *Supra* note 40.
[47] C-34/10, Judgment of the Court (Grand Chamber) 18 Oct. 2011, also *available at* http://curia.europa.eu/juris/liste.jsf?language=en&num=C-34/10 (last visited July 25, 2014).
[48] Article 6(1) states that, "[i]nventions shall be considered unpatentable where their commercial exploitation would be contrary to ordre public or morality"; and Article 6(2) states that, "[o]n the basis of paragraph 1, the following, in particular, shall be considered unpatentable:
(a) processes for cloning human beings;
(b) processes for modifying the germ line genetic identity of human beings;
(c) uses of human embryos for industrial or commercial purposes". *Supra* note 40.
[49] See ch. 3.1.2.4 ARE THEY SUBSTITUTE OF EACH OTHER OR DIFFERENT FROM EACH OTHER?
[50] 35 U.S.C. § 103 (2013).

The non-obviousness requirement was applied in the case of *Graham v. John Deere Co.* (1966) by the U.S. Supreme Court.[51] However, if it (the non-obviousness requirement) is strictly applied for the protection of hSCI, some of the subsequent inventions and second medical applications will not qualify for the patent protection, as they might be insubstantial invention.

However, it cannot be decisively said that *novelty* and *non-obviousness/inventive step* apparent in an invention will be adequate to support the patent survive the legal battles. A patent may fail to survive entirely or partially in the post grant proceedings at the patent office or later at Court. The intricate parts of the claims may not contain enough invention/innovation to justify the novelty and non-obviousness in a given case. After the first isolation and derivation of ES cells in non-human primate by the scientist James Thomson in 1995 of Wisconsin Alumni Research Foundation (WARF), the WARF became the assignee of many US patents on non-human primate and human ES cell derivation process and derived cells in the succeeding years. The relevant WARF patents are following:

- The United States Patent No. 5,843,780, issued on December 1, 1998 for "[p]rimate embryonic stem cells;"[52]
- The United States Patent No. 6,200,806, issued on March 13, 2001 for "[p]rimate embryonic stem cells;" [53]
- The United States Patent No. 7,029,913, issued on April 18, 2006 for "[p]rimate embryonic stem cells;"[54] and
- The United States Patent No. 7,442,548, issued on October 28, 2008 for "[c]ulturing human embryonic stem cells in medium containing pipecholic acid and gamma amino butyric acid."[55]

Although the US Patent No. 5,843,780 and the US Patent No. 6,200,806 survived till date, the US Patent No. 7,029,913, issued on April 18, 2006 has been tangled with oppositions. However, WARF patents generated much debates, arguments and protests. They have faced oppositions from the public interest groups. Nevertheless, they survived as patent keeping the question "if human embryonic stem cells should be patented to allow exclusive right at all" alive. Easy access to these inventions/innovations are very important for the other researchers to be able to develop "biological drug products".[56] In 2013, the WARF's US Patent No. 7,029,913 was challenged in the United States Court of Appeal for the Federal Circuit by the Consumer Watchdog, a nonprofit organization, in the

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[51] Graham v. John Deere Co. of Kan. City, 383 U.S. 1 (1966).

[52] United States Patent and Trademark Office, *USPTO Patent Full-Text and Image Database, available at* http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=%2Fnetahtml%2FPTO%2Fsrchnum.htm&r=1&f=G&l=50&s1=5,843,780.PN.&OS=PN/5,843,780&RS=PN/5,843,780 (last visited Nov. 20, 2014).

[53] The very patent also claimed to have disclosed the "know-how" for the derivation of human ES cells. United States Patent and Trademark Office, *USPTO Patent Full-Text and Image Database, available at* http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=%2Fnetahtml%2FPTO%2Fsrchnum.htm&r=1&f=G&l=50&s1=6,200,806.PN.&OS=PN/6,200,806&RS=PN/6,200,806 (last visited Nov. 20, 2014).

[54] United States Patent and Trademark Office, *USPTO Patent Full-Text and Image Database, available at* http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=%2Fnetahtml%2FPTO%2Fsrchnum.htm&r=1&f=G&l=50&s1=7,029,913.PN.&OS=PN/7,029,913&RS=PN/7,029,913 (last visited Nov. 20, 2014).

[55] United States Patent and Trademark Office, *USPTO Patent Full-Text and Image Database, available at* http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=%2Fnetahtml%2FPTO%2Fsrchnum.htm&r=1&f=G&l=50&s1=7442548.PN.&OS=PN/7442548&RS=PN/7442548 (last visited Dec.10, 2014).

[56] FDA's "Compliance Program Guidance Manual Chapter – 45 Biological Drug Products" mentions stem cells and cell therapies as "biological drug products" (U.S. Food and Drug Administration: Compliance Program Guidance Manual (CPGM) 2014).

case of *Consumer Watchdog v. Wisconsin Alumni Research Foundation* (2013) claiming that the inventions are not eligible for patenting, but the appeal was dismissed on June 4, 2014. [57] Although the Appellant Consumer Watchdog claimed that the inventions *lack novelty and inventive steps*, they also indicated that patenting those inventions by WARF *resulted to burden on the taxpayers' money*.[58] But the rejection of Appeal did not highlight any of those (patentability criteria and implications of patenting) issues; rather the absence of *locus standi* of the Appellant as an "aggrieved person" was shown as the justification for the rejection of Appeal by the US Court of Appeal for the Federal Circuit.[59] Therefore, those inventions have not yet failed the test of the novelty and inventive step requirement and their justification of patenting being inventions from public funded research[60] shall remain as a "debate" to be resolved probably by a Supreme Court's (US) ruling in future.

Feldman and Furth made the following discussion on the application of non-obviousness standard in the field of iPSC inventions in the USA:

> In the years leading up to 2007, the Federal Circuit had been applying the so-called TSM test[61] for determining obviousness. According to the test, an invention would not be ruled patentable as a combination of information available in the prior art unless that art contained a specific teaching, suggestion, or motivation to combine the prior art. In the 2007 case of *KSR Int'l Co. v. Teleflex Inc.*, the U.S. Supreme Court rejected the Federal Circuit's application of the TSM test in a case concerning automobile gas pedals. The Supreme Court ruled that the test had been applied too rigidly. The Court also held that the Federal Circuit also erred in concluding that application of the TSM test was mandatory. (2010, 31; footnote added, footnote omitted)

It seems that the U.S. Supreme Court has a softer approach in determining the non-obviousness standard. On the other hand, the EPO or CJEU on patentability issues had been apparently more strict in the recent past. It is more likely that technical intervention involved in reprogramming of the iPSC's early inventions may survive the non-obviousness standard in some patent offices very well. But the downstream inventions in iPSC making small variations in iPSC generation methods and application might not encompass substantial "inventive step." Therefore, it is necessary that the claim language of each invention is very precise to its inventive aspect. An overly broad claim may block the subsequent inventions to get a patent.

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[57] Case 13-1377, Fed. Cir. 2013.
[58] Consumer Watchdog v. Wisconsin Alumni Research Foundation, *supra* note 57.
[59] *Id.* (June 4, 2014).
[60] The inventions of the US Patent No. 7,029,913, which was challenged by the Consumer Watchdog, was the result of the research sponsored by the US Federal Government (US Patent No. 7,029,913, issued on April 18, 2006). United States Patent and Trademark Office, *USPTO Patent Full-Text and Image Database*, *available at* http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=%2Fnetahtml%2FPTO%2Fsrchnum.htm&r=1&f=G&l=50&s1=7,029,913.PN.&OS=PN/7,029,913&RS=PN/7,029,913 (last visited Nov. 20, 2014).
[61] Teaching-Suggestion-Motivation Test.

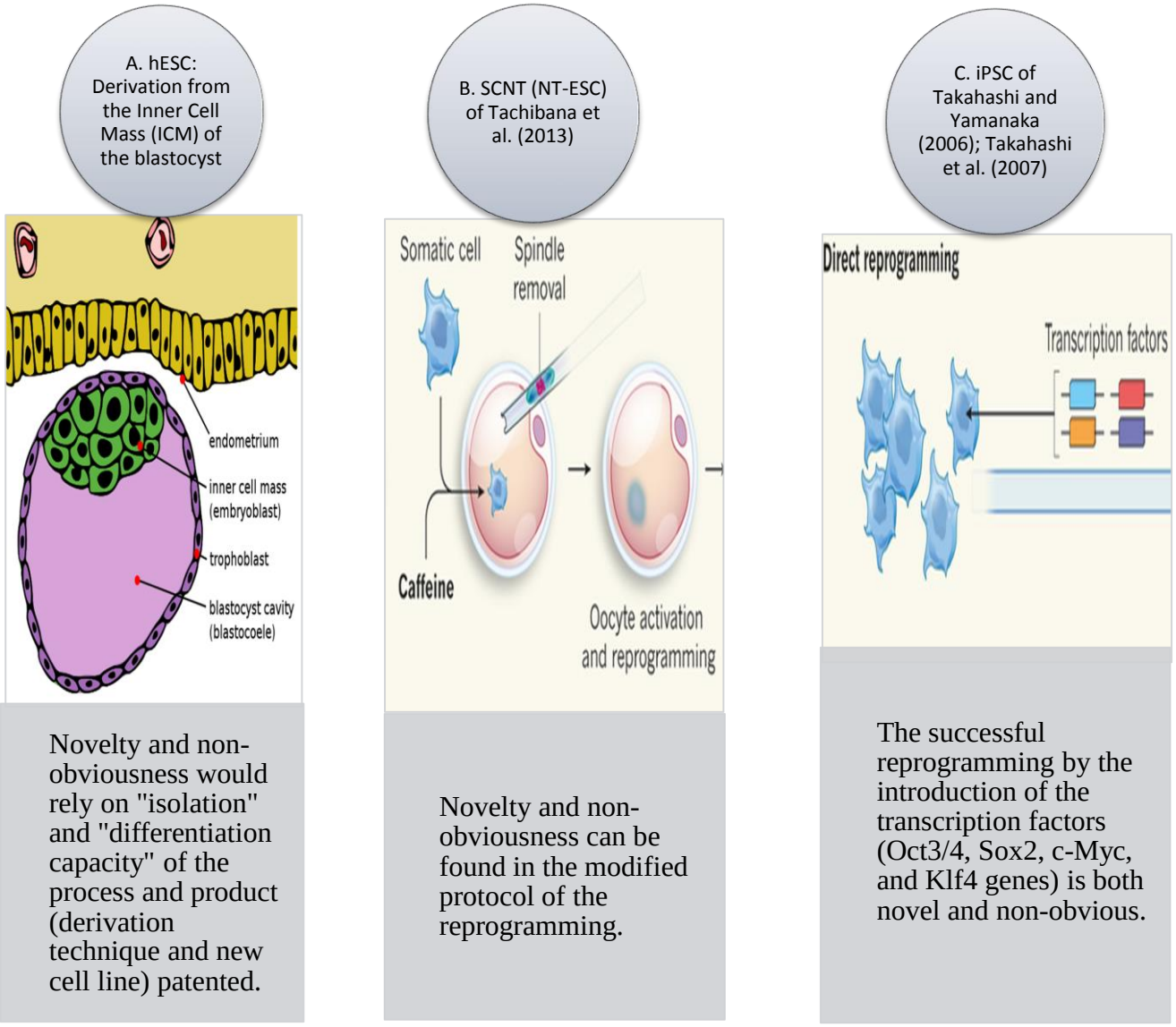

Fig. 4.1 Novelty and Inventive Step (Non-obviousness) in hESC (A) (Illustration from Wikipedia: Inner cell mass 2014), SCNT (Embryo Cloning) (B) and iPSC (C) (Figure 1, Mummery and Roelen 2013, 174)

4.3.3 INDUSTRIAL APPLICATION

Takahashi et al. (2007) published "Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors" in 2007. The clinical trial in human for this iPSC invention started in 2014. At the Institute for Biomedical Research and Innovation, Kobe, Japan, a 70 years old woman as the participant of this clinical trial received the first graft of iPSCs on September 12, 2014 (Stem Cells Portal: AMD Patient Receives First Induced Pluripotent Stem Cell Graft 2014). The industrial and commercial application of this technology will be in the market after the safety and efficacy is proven by this clinical trial. The observation period of this study is 3 years. (Stem Cells Portal: World's First Induced Pluripotent Stem Cells Clinical Study on Humans Launches in Japan, 2014). The patent shall last 20 years from the invention was first proclaimed in mouse in 2006 (Takahashi and Yamanaka 2006) and in human in 2007 (Takahashi et al. 2007). The year in which "human" received the transplant for the first time is 2014 (clinical trial). The industrial and commercial application may begin after the safety and efficacy of the transplant is proved. The study has estimated observation period of 3 years. Therefore, the technology will have very short time for commercial exploitation after it enters the clinic for-profit basis. Mathews, Deegan, and Bubela (2013, 508) wrote: "Therapies may take between 10 and 15 years to reach the clinic—a timespan that will likely be even longer for cell-based interventions— while patent terms extend for 20 years plus marginal extensions to account for regulatory approval processes and necessary clinical studies."

Many of the ES cell derivation patents by the WARF will be useful for the other stem cell and biomedical researches. As product to arrive in the clinic, many of the hESC based inventions will have to wait long time. While the process patents already in existence for the ES cell isolation and derivation, those inventions remain useful for the downstream researchers. But those patents will make them (the downstream researchers) to take a license for their commercial exploitation, if they (the downstream researchers) are successful in making any disease specific inventions. Therefore, the meaning of "industrial application" of the patents on the primary (first generation) hSCI is yet *not the strict application as cure for a condition or disease*; rather many of them are inventions having *utility for further research* targeted to product development. However, it is worth reiterating that the derivation of embryonic stem cell is possible through various methods.

Steven D Schwartz et al. (2012, 713) mentioned in their publication on the trial of ESC[62] for the macular degeneration:[63] "It has been 13 years since the discovery of human embryonic stem cells (hESCs). Our report provides the first description of hESC-derived cells transplanted into human patients."

[62] Advanced Cell Technology (substituted corporate name Ocata Therapeutics, Inc.), who has funded this study, patented (e.g., United States Patent No. 8,742,200, issued on June 3, 2014) derivation of ES cells from the blastomere cell of the pre-implantation stage embryo (ES cells from biopsied embryo).

[63] Macular degeneration is a major cause of blindness.

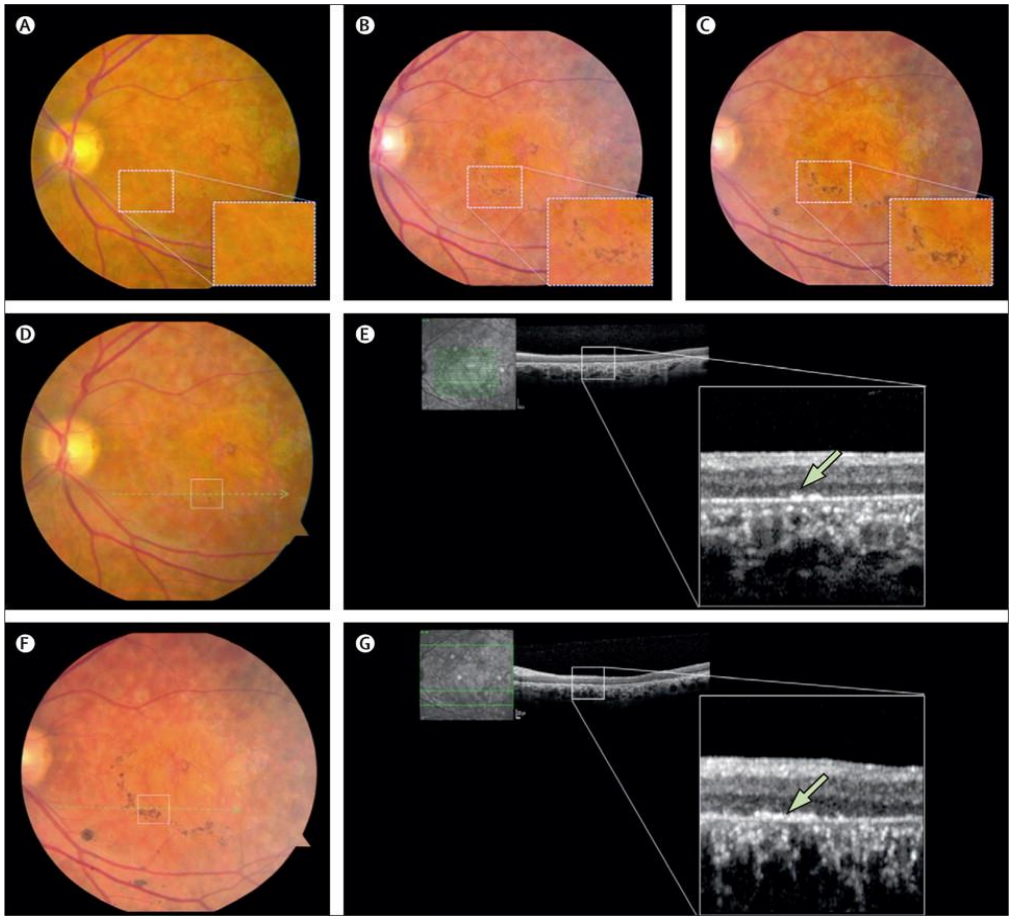

Fig. 4.2 "Images of the hESC-RPE transplantation site in the patient with Stargardt's macular dystrophy" (Figure 4, Schwartz et al. 2012, 718)

In all cases, patent succeeds the claimed invention, but precedes the clinical trial. The time lost in clinical trial, is lost from the term of protection of the patent.

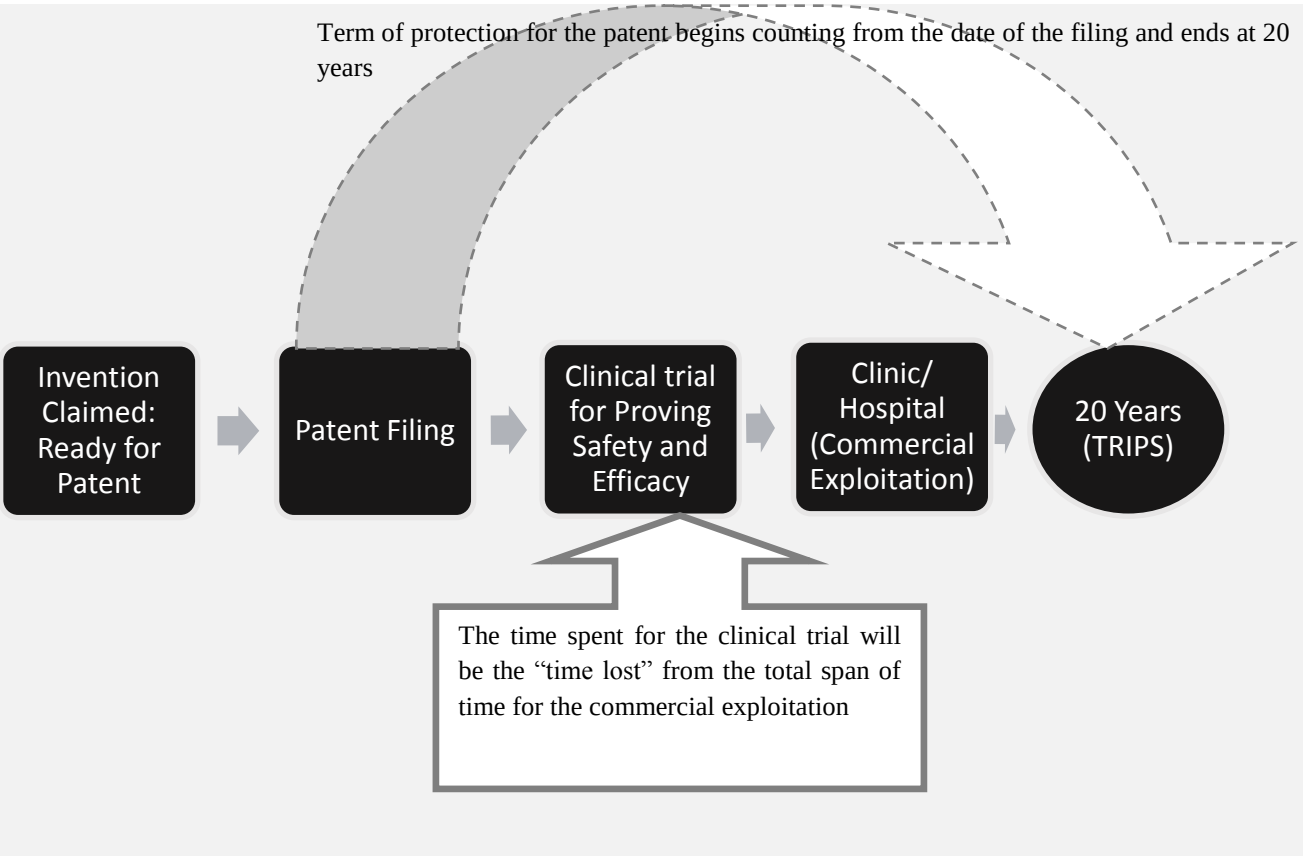

Fig. 4.3 Term of protection continues towards its end, beginning from the date of patent filing

The apprehension of losing time also can push the companies to hurry up to reach to the market. The diverse industrial applications may not all fit the ideal interpretation of "industrial application" of the patentable inventions.

The patented technique of production of retinal pigment epithelium (RPE) cells from human embryonic stem cells by Advanced Cell Technology (Ocata Therapeutics, Inc.) was given orphan drug status for the RPE cells in 2010 (American Macular Degeneration Foundation: Stargardt Disease 2014).[64] There are two implications of this "orphan drug status", i.e., (a) availing the benefits of the tax reductions; and (b) in the phase III clinical trial, FDA may recognize that the number of 1000 participants may not be available/possible due to the lower number of population affected by the disease (American Macular Degeneration Foundation: What is Orphan Drug Status? 2014).

The age related Macular Degeneration is currently "affecting more than 10 million Americans" and a major cause of vision loss in the population over the age of 55 (American Macular Degeneration Foundation: What is Macular Degeneration? 2014). With the growing number of aging population in the industrialized world, the number of population affected by the Age-related Macular Degeneration (AMD) will dramatically increase. The Archives of Ophthalmology of National Eye Institute (NEI), USA documented in the Vol. 122, dated April 2004, that the prevalence of Advanced AMD is witnessed in a total of 1,749,000 (1.5%) persons and Intermediate AMD in 7,311,000 (6.1%) persons (among the age group of 40 and above) (National Eye Institute (NEI): Statistics and Data, Prevalence

[64] Their initial study report on safety and efficacy by Schwartz et al. (2014, 2--3) admitted a low sample size of the 18 patients as the participants.

of Blindness Data 2014). In 10 years' time, from then (2004), the disease has by now affected more American lives. Needless to mention that it has affected population in other parts of the world too.

Industrial application of the invention is a requirement of the patent and it is possible to fulfill this requirement. But how the investors are transforming their invention into the "industrial application" has completely pulled the "incentive for innovation" and "health care" to the back seat and pushed the commercial character of the companies forward. Are the companies giving new look and meaning to the patent itself? Having just an "industrial application" to get a patent is not enough, for diseases affecting lives. The patent law also need to take into account "how the industrial application" is materialized/translated by the patentee. A new meaning of "industrial application" is needed.

Therefore, the hSCI will have less difficulty to fit into the patentability requirements in the present conditions. But a lot more concerns remain on how the patented technology will affect the health care receivers. Shall patent monopoly allow access to the therapy or restrict it? Shall patent bring enough incentive for the inventors and assignee, if the therapy reach to the market after the substantial term of protection is lapsed in the last phase of clinical trial? Will patent not hinder downstream research? Will the health care tourism increase as a result of divergent legal framework having differing interpretation of "ethical" issues on patentability? Therefore, these questions remain the challenge for the IP protection of hSCI under the umbrella of patent, rather than satisfying the patentability requirement for those inventions/innovations. However, the patentability has also been questioned in some cases.

4.4 PATENT RELATED CONCERNS

Patent is commonly referred as an incentive that encourages the invention/innovation; but it also can cause hindrance for the development of the new invention (Winickoff, Saha, and Graff 2009, 88). An exclusive right is granted in favor of the inventor and/or assignee, not only to encourage them, but also to exclude the "free riders" who might steal the right owners' labor and investment. But IPR in which form is perfect for the hSCI?

Question no. 6 asked the respondents if they "think patent protection as it exists today is the best way to provide incentive to human stem cell based inventions/innovations". The *Major Key Themes* derived from the responses to question no. 6 show how they commented about the current patent system:[65]

- Patent protection may not be sufficient for biotechnology products;
- "Ad hoc data exclusivity rights";
- Going further than this (exceeding 20 years) would affect access to therapy for the patients in less developed countries;
- "Realization and understanding";
- "Life is already in existence";
- hESC research has ethical constraints;

[65] Some of the words/phrases used/mentioned within quotation in the major key themes and their interpretations are the exact words/phrases used by the respondents. Appendix V: Qualitative Analysis (Qualitative Content Analysis (QCA)).

The questionnaire mentioned that, "the identity of the participants shall be kept anonymous, unless required to prove the authenticity of the study." Appendix II: Questionnaire.

- Litigations and oppositions are becoming more common;
- "Protecting the moral rights"; "not for commercialization";
- Researchers are driven by "curiosity" and "altruism";
- Noble purpose behind the innovation;
- Skepticism about the appropriateness of the patent system for life sciences;
- Possible adverse social effects;
- Controversies around patenting second medical application of known drugs.

The interpretation of the *Major Key Themes* derived from responses to question no. 6 can be found in ch. 5.

The hSCR is a relatively new field and continuously evolving. While large numbers of promised applications are at clinical trial or simply at research stage, a lot of patents are already granted in the emerging technologies of stem cell researches (Winickoff, Saha, and Graff 2009, 75).

The early patents may expire before the products are at the market or they may cause hindrance to the downstream researches by requiring licenses. The "infringement litigation" and the "settlement" may eat up the profits, a patent on a downstream invention might have made. Bergman and Graff thought that "patent thicket" may "slow and skew the overall development of new technical applications" (2007, 419). Gaetan de Rassenfosse and Bruno van Pottelsberghe de la Potterie conducted an empirical study on "R&D–patent relationship" and found:

> A better *quality of education* is a factor that substantially improves researchers' productivity in a country, and hence their observed patenting performance. […]. *S&T policies* also come into play: the higher the share of business R&D and the more resources are allocated to researchers, the more productive the research efforts will be.
>
> Regarding the propensity to patent, the design of IP systems matters. Several dimensions of a patent system, including the number of patentable subject matters, restrictions, enforcement mechanisms, and especially its fees, all affect a country's patenting performance. (Rassenfosse and Potterie 2009, 788; italics added)

Patent system in post TRIPS era is an economic tool. The humanitarian implication of the strong patent protection of inventions in health care sector is largely ignored. The different circumstances and needs of the countries and their population are hardly taken into consideration.

The respondents were asked (question no. 13): "Do you think public opinion should be sought and be given importance after the invention/innovation is put to the market for commercial exploitation, in order to measure the impacts of the IPR protected invention/innovation on the health care receiver?".

The *Major Key Themes* derived from responses to question no. 13:[66]

- Public in general are not informed enough to give valuable feedback;
- Skeptical about the issue of consulting with the public;

[66] *Supra* note 65.

- "Obvious public outcry";
- Information should be made available to the consumers *a priori*;
- Embryo source is central to public interest and not access, affordability, safety or efficacy of the therapy (in case the therapy is developed from hESC);
- Civil society should have the legal means;
- Pre-commercial exploitation public consultation.

The comments showed indication that public are not really well-informed about the IP and its effect. The interpretation of the *Major Key Themes* derived from responses to question no. 13 can be found in ch. 5.

The application of stem cell based therapies will range from eye care to heart diseases. Soon after the application arrives the clinic, they may become essential to health care. How much profit a drug developer may be allowed to make, by exploiting the patent, should be a legislative concern.

Arif Jamil made a discussion on the inherent character of the "patent" and explored if it is meant to treat the protected invention as "property":

> Patent right which can give rise to monopoly was intended to encourage innovation by providing an incentive and was meant to protect the *rights of the inventors* (Usselman and John, 2006, p.99, 116; Ventose, 2011, p.14). It is a tool for recovery of investment and generating money for future research. Inventor alone is not enough to commercialise an invention. Public or private funds may be needed for putting the invention into market. Therefore, the *assignee* or the investor is the dominant player whose interests the protection tool ultimately secures. Therefore, a patent makes sure that the system assists him to use the invention in profitable manner by excluding the competitors. Some of the scholars see patent as a 'property right' (Dam, 1994, p.247). However, the purpose served by the patent and the profits made varies from industry to industry. […]. Bessen and Meurer (2008) indicate that the changes in the features of technology reduces demand of the earlier version, and the value of the patent deteriorates (Bessen and Meurer, 2008, p.100). But in the health care related industries, the patents are more effective than other disciplines of technology (Bessen and Meurer, 2008, p.106). (2013a., 28--29; Italics added)

The patent system is so focused on the "commercial exploitation" and "exclusiveness" of the right of the assignee that the protected invention becomes more like a property.

In order to confirm a stem cell based product as proven therapy, it goes through the phases of clinical trials. Once the acceptable levels of safety and efficacy in defined number of subject/patients is observed, then it is manufactured on a larger scale, i.e., on a commercial level. Based on the frequency of the disease in question in the general population, this level of commercialization would vary. Therapy to some common diseases would be produced in bulk quantities while for treating rare diseases, it is usually produced at a smaller scale and often customized to individual patient.

Patent is indeed a property right owned by an individual or entity for a certain duration of time. Only if, from the research and innovation to the commercialization, all is conducted with public funding

and the services distributed through public structures, the delivery of service can be executed in non-commercial manner. In that case, the invention will require only recognition; no exclusive rights of commercialization will be needed. The commercialization is an integral phenomenon of private investment in research, innovation. The patent is a tool that may encourage private investment in research and apparently shows a way to secure the return of the investment.

The respondents were asked: "Do you think that a new protection mechanism/framework can be / should be developed within the purview of intellectual property law (IPR), separate from patent, for the inventions/innovations that use biological materials of human origin and targeted to health care?".[67] The *Major Key Themes* derived from responses to that question (no. 7) show that many of the experts are inclined to reduced commercialization of health care related inventions:[68]

- New creation cannot be made within the realm of life science;
- hSCI cannot be patented;
- Health care transformed into business;
- Stakeholders of health care should focus on how to provide affordable care and therapy to people;
- Reduced commercialization;
- Does not support any protection framework with a commercial feature;
- Government's money;
- Research targeted to health care is done for humanity;

The Interpretation of the *Major Key Themes* derived from responses to question no. 7 can be found in Ch. 5.

4.4.1 PROPRIETARY NATURE OF THE HUMAN STEM CELL BASED INVENTION/INNOVATION

Some of the important patents on hSCI reveal that the industry is heavily influenced by the private and autonomous entities such as companies and universities. It is unlikely that these private entities will offer therapies to the patients on a "not for profit" basis. In fact, they are marketing their inventions before the safety and efficacy of those inventions are proven from the clinical trial. The patents they have are the "property" they own and they shall commercially exploit it as soon as the safety and efficacy of the methods are proven. Since they have received patent before (in some instances long before) the clinical trial is over, some of them may ask for new patents by showing some insubstantial improvement to keep the exploitation of the invention possible for a plausible term of protection.

However, the assignees of some of the remarkable US Patents for/from the human stem cell industry in the recent past, holding the commercial interest, are:

[67] Question No. 7.

Stem cell based inventions require the use of biological materials of human origin.

[68] *Supra* note 65.

A. Wisconsin Alumni Research Foundation (Madison, WI, USA) holds patent for the isolation of primate ES cells while claiming that the same procedure will make isolation of human ES cells possible.

- United States Patent No. 6,200,806 was issued on March 13, 2001 having the Wisconsin Alumni Research Foundation (Madison, WI, USA) as the assignee for "[p]rimate embryonic stem cells" (US Patent No. 6,200,806, issued on Mar. 13, 2001). The details of the patent is claiming the invention as likely methods for isolation of human embryonic stem cells. The isolation of ES cells in this invention was originally conducted on primates.

B. Kyoto University, Japan holds iPSC (Induced Pluripotent Stem Cell) patents.

- United States Patent No. 8,048,999 was issued on November 1, 2011 having the Kyoto University, Japan as the assignee for the "[n]uclear reprogramming factor" (US Patent No. 8,048,999, issued on Nov. 1, 2011);
- United States Patent No. 8,058,065 was issued on November 15, 2011 having Kyoto University, Japan as the assignee for the methods of generating iPSC by the nuclear reprogramming factor "Oct3/4, Klf4, c-Myc and Sox2" (US Patent No. 8,058,065, issued on Nov. 15, 2011);
- United States Patent No. 8,129,187 was issued on March 6, 2012 having the Kyoto University, Japan as the assignee for the "[s]omatic cell reprogramming by retroviral vectors" (US Patent No. 8,129,187, issued on Mar. 6, 2012).

C. International Stem Cell Corporation (a biotechnology company) based in California, USA holds hpSC (Human Parthenogentic Stem Cell) patent.

- United States Patent No. 8,420,393 was issued on April 16, 2013 having International Stem Cell Corporation as the assignee for "[g]eneration of an autologous stem cell library from human oocytes parthenogenetically activated by high or low oxygen tension" (US Patent No. 8,420,393, issued on Apr. 16, 2013).

D. The New York Stem Cell Foundation, NY, USA (a non-profit organization) holds a patent on the derivation of pluripotent stem cells by Nuclear Transfer.

- United States Patent No. 8,748,178 was issued on June 10, 2014 having the the New York Stem Cell Foundation (New York, USA) as the assignee for "[m]ethod for producing pluripotent stem cells" by activating the human oocyte, without removing the genome of the oocyte (US Patent No. 8,748,178, issued on June 10, 2014).

E. Advanced Cell Technology, Inc., (Ocata Therapeutics, Inc.), a biotechnology company, based in Marlborough, Massachusetts, USA holds the patent on ESC derived from the Blastomere cell of pre-implantation stage embryo.

- United States Patent No. 8,742,200 was issued on June 3, 2014 having the Advanced Cell Technology, Inc. (Marlborough, MA) as the assignee for the "[d]erivation of embryonic stem cells and embryo-derived cells" (US Patent No. 8,742,200, issued on June 3, 2014).

F. Oregon Health & Science University (OHSU), Oregon, USA, hosting the lab of Shoukhrat Mitalipov is likely to get US patent in near future for derivation of ESCs by SCNT (Somatic Cell Nuclear Transfer) a.k.a. NT-ESC.

- Masahito Tachibana et al. (2013) published "Human Embryonic Stem Cells Derived by Somatic Cell Nuclear Transfer". It is claimed to be the first "successful" derivation of hESC

> by SCNT. The most probable assignee of this invention is the Oregon Health & Science University (OHSU), USA.

Some of the researches by the universities may be funded/covered by the Government grants but the Government's grants regulate the research ethics only. The funding institutions of the Governments do not usually conduct any investigation on the implications of patent protection of these inventions over the health care receivers. Once the research institution gets the inventions patented, it is essentially their intellectual property. In the light of the abovementioned patents, it appears that even the inventors get the recognition as the *inventor only*, not any share in the commercial interest. The recent patent landscape of the most advanced human stem cell techniques reveal that the commercial interests are clearly not dominated by the scientist or any "not for profit" organization, rather are the exclusive intellectual property of the *assignee* institutions. However, the New York Stem Cell Foundation proclaims itself as a non-profit organization (The New York Stem Cell Foundation (NYSCF) 2014). Although an entity may proclaim itself as a non-profit organization, it is free to exploit the patent commercially. The WARF also proclaims as "private, nonprofit patent and licensing organization for the University of Wisconsin" (Wisconsin Alumni Research Foundation (WARF) 2014), but it did have defended its ES cell patents for the commercial reasons and seeking "commercial partners" for its patents (Wisconsin Alumni Research Foundation (WARF): Drug Discovery: 2014). In 2006, WARF was issued another US Patent (No. 7,029,913) for isolation of human ES cells which received oppositions both at USPTO and the United States Court of Appeals for the Federal Circuit.[69] The United States Government in its brief in the case of *Consumer Watchdog v. Wisconsin Alumni Research Foundation*, argued that the appeal should be dismissed and pleaded that the Appellant Consumer Watchdog neither have any concrete interest in the US Patent No. 7,029,913 nor aggrieved by it.[70] Clearly representing the consumers' or taxpayers' interest is not enough to contest the patentability of an invention "on the technicalities or its implication" at the US Court of Appeals for the Federal Circuit, as the appeal was eventually dismissed for lack of *locus standi* of the Consumer Watchdog as the Appellant.[71] Despite WARF patents on ES cell derivation received many oppositions, they survived till date. It is worth quoting from the patent (US Patent No. 7,029,913) itself the following statement about the source of the funding behind the inventions: "This invention was made with United States *government support* awarded by NIH NCRR Grant No. RR00167. The United States government has *certain rights* in this invention" (US Patent No. 7,029,913, issued on April 18, 2006; italics added).[72] The report of the NIH to the United States Congress of 2001 regarding "A Plan to Ensure Taxpayers' Interests are Protected" stated:

> In 1980, […] Congress enacted two laws that encourage government owned and government funded research laboratories to pursue commercialization of the results of their research. These laws are known as the *Stevenson-Wydler Act* and *the Bayh-Dole Act*. Their goal is to promote *economic development, enhance U.S. competitiveness*, and benefit the public by *encouraging the commercialization of*

[69] Consumer Watchdog, a nonprofit organization, challenged the patentability of the inventions in the case of *Consumer Watchdog v. Wisconsin Alumni Research Foundation*. *Supra* note 57.
[70] Case 13-1377, Doc. 43, Fed. Cir. 2013 (Jan. 17, 2014).
[71] Consumer Watchdog v. Wisconsin Alumni Research Foundation, Case 13-1377, Fed. Cir. 2013 (June 4, 2014).
[72] United States Patent and Trademark Office, *USPTO Patent Full-Text and Image Database*, *available at* http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=%2Fnetahtml%2FPTO%2Fsrchnum.htm&r=1&f=G&l=50&s1=7,029,913.PN.&OS=PN/7,029,913&RS=PN/7,029,913 (last visited Nov. 20, 2014).

> *technologies* that would otherwise not be developed into products due to *lack of incentives*.[…]. The Bayh-Dole Act was enacted to allow federal agencies to *secure patent rights* and convey them to *commercial entities* through licensing[…]. A key provision of the Act is that it provides grantees and contractors, both for-profit and not-for-profit, the authority to *retain title* to government-funded inventions, and charges them with the responsibility to use the patent system to promote utilization, commercialization, and public availability of inventions.[…]. To accomplish the transfer of technology, NIH and NIH-funded recipients *typically seek patent protection* for inventions arising out of this basic research and license the rights to private entities to *promote commercialization*. Thus, private entities interested in practicing an invention in which they have no ownership may obtain rights to use and commercialize the invention by entering into a *licensing agreement* with the patent owner. A license is a contract with binding commitments on each party, usually *involving compensation* (i.e. royalties, milestone payments, etc.). (NIH Intellectual Property Policy: Protecting Taxpayers' Interests (07/2001) - NIH Response to the Congressional Committee Report Request for a Plan to Ensure Taxpayers' Interests are Protected 2014; italics added)

This narrative of the NIH policy highlights the issues of *incentive for innovation*, *commercialization* and *competitive advantage* and patent is believed to be the tool to achieve them. But the wider access to the patented technology by the people, developed by the taxpayers' money is not anywhere at the forefront of the laws and policy. NIH policy summary on sharing and disseminating the biomedical research resources also shows that access to research by the scientific community and dissemination through contractual arrangement are important considerations:

> Access to research tools is a prerequisite to continuing scientific advancement. Ensuring broad access while preserving opportunities for product development requires thoughtful, strategic implementation of the Bayh-Dole act. The NIH urges Recipients to develop patent, license, and material sharing policies with this goal in mind, realizing both product development as well as the continuing availability of new research tools to the scientific community.[73]

Although the invention of US Patent No. 7,029,913 was developed with the Federal funding, the patent will enable the assignee to exploit it commercially. The ultimate goal and motive of securing the commercial interest over the invention through the patent is to make the *protected subject* (the invention/innovation itself) a property of the assignee. However, the stakeholders express their goals and visions in different ways:

- The Wisconsin Alumni Research Foundation (WARF) says: "The Wisconsin Alumni Research Foundation (WARF) is seeking commercial partners interested in a purified preparation of pluripotent human embryonic stem cells." (WARF: Through Technologies 2014).

- Center for iPS Cell Research and Application (CiRA), Kyoto University states: "Goals for 2020: [...] Establish basic iPS cell technology and secure the associated intellectual property

[73] Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical Research Resources: Final Notice, 64 Fed. Reg. 72090--72096 (Dec. 23, 1999).

rights [...].” (Center for iPS Cell Research and Application: Message from the Director 2014).

- International Stem Cell Corporation (ISCO) says: “In the medium term, revenue could be generated from universal stem cell bank franchises […] and, longer-term, will provide the company with royalty from sales of each successful, hpSC-derived cellular therapeutic.” (International Stem Cell Corporation: Stem Cell Bank 2014).

- The New York Stem Cell Foundation (NYSCF) claims: “Building a bank of 2,500 stem cell lines […]. This revolutionary global resource will equalize access for safe and effective medicine for EVERYBODY including underserved populations.” (The New York Stem Cell Foundation: NYSCF Research 2014).

- Advanced Cell Technology, Inc., says: “Ocata Therapeutics, Inc. […], formerly named Advanced Cell Technology, is a clinical stage biotechnology company focused on the development and commercialization of new therapies in the field of regenerative medicine.” (Ocata Therapeutics: Company Overview 2014).

- Center for Embryonic Cell and Gene Therapy, Oregon Health & Science University (OHSU) claims: “Philanthropic gifts from corporations and foundations also provide critical money for our new research initiatives on human embryo and stem cell research.” (Center for Embryonic Cell and Gene Therapy: Support Our Lab 2014).

The larger quantity[74] of the stem cell patents under the possession of private sector may heavily influence the industry to achieve the commercial goals rather than serving the health care objectives. The assignee of several first generation inventions are corporations, universities and research institutes.[75] From the cited examples, the assignees (US patent either already granted or likely to be granted) found are:

- Wisconsin Alumni Research Foundation (WARF), Madison, USA;
- Kyoto University, Japan;
- International Stem Cell Corporation, California, USA;
- New York Stem Cell Foundation, NY, USA;
- Advanced Cell Technology, Inc. (Ocata Therapeutics, Inc.), Marlborough, Massachusetts, USA; and
- Oregon Health & Science University (OHSU), Oregon, USA.

These organizations/institutions will be able to collect royalties from licensing and make profit from the exploitation of the inventions, as those inventions will serve as their property.

The respondents were asked (question no. 10): “Who, according to your opinion, should be entitled to the intellectual property rights (IPR) of human stem cell based inventions/innovations?”. The

[74] Bergman and Graff found that, “[o]f US granted stem cell patents, 44 percent were assigned to public sector entities and 56 percent to private sector entities” (2007, 421).

[75] Even if the research institute have received the Government funding for research, it is allowed to do commercial exploitation through patent.

Major Key Themes derived (from the comments of the experts/respondents) from responses to question no. 10 are:[76]

- Who will own the IPR shall depend on contractual arrangement as determining factor;
- Donor of cell line should receive a compensation;
- Scientist/inventor and patients;
- "Moral right", not an economic right;
- Employer organization/university makes no intellectual contribution to the hSCI;
- Entitlement determined by funding sources.

Many of the comments had brought the humanitarian aspects of innovation to the fore. However, the interpretation of the *Major Key Themes* derived from responses to question no. 10 can be found in ch. 5.

4.4.2 REGULATORY DATA EXCLUSIVITY, BOLAR EXEMPTION AND COMPULSORY LICENSE

TRIPS Agreement does not use the term "compulsory license" but there are some provisions under the title of "[o]ther [u]se [w]ithout [a]uthorization of the [r]ight [h]older" in Article 31 that serves similar purpose of allowing the use (of patented invention) in *limited circumstances* and *conditions being fulfilled*.[77] In order to avail the options of Article 31, the company or person seeking the license/approval/permission to use the patent must have tried to "obtain authorization from the right holder on reasonable commercial terms and conditions" and was unsuccessful.[78] This requirement may be waived for "national emergencies", "other circumstances of extreme urgency" or "public non-commercial use" or use by the government or to remedy an anti-competitive practice.[79] However, Doha WTO Ministerial Declaration on the TRIPS Agreement and Public Health expressly use the term "compulsory license."[80] Article 30 of the TRIPS Agreement known as "Bolar" provision is implemented in national laws to allow the generic drugs' manufacturers to use the patented information for availing the marketing authorization from the regulatory authority. But the generic cannot enter the market until *the patent* and *the data exclusivity right* has expired.

Article 10 of the Directive 2004/27/EC states: "A generic medicinal product authorised pursuant to this provision shall not be placed on the market until ten years have elapsed from the initial

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[76] *Supra* note 65.
[77] Agreement on Trade-Related Aspects of Intellectual Property Rights, Apr. 15, 1994, Marrakesh Agreement Establishing the World Trade Organization, Annex 1C, 1869 U.N.T.S. 299, 33 I.L.M. 1197 (1994) [hereinafter TRIPS Agreement].
[78] TRIPS Agreement art. 31(b).
[79] TRIPS Agreement art. 31(b)(k).
[80] World Trade Organization, Ministerial Declaration on the TRIPS Agreement and Public Health of 14 November 2001, art. 5 (b)(c), WT/MIN(01)/DEC/2, [hereinafter Doha Declaration], also *available at* http://www.wto.org/english/thewto_e/minist_e/min01_e/mindecl_trips_e.htm.

authorisation of the reference product." [81] Apart from this 10 years, one additional year of protection is available for the second medical application of the already protected substance.[82] The Bolar provision can be found in Article 10(6) stating that, "[c]onducting the necessary studies and trials with a view to the application of paragraphs 1, 2, 3 and 4 and the consequential practical requirements shall not be regarded as contrary to patent rights or to supplementary protection certificates for medicinal products."[83]

Anthony Tridico revisited and summarized the prevailing legal and policy landscape surrounding the Bolar provision, Regulatory Data Exclusivity (RDE) and generic drug manufacturing and commented:

> In the US, the Hatch-Waxman Act established a regulatory framework to encourage the marketing of generic pharmaceutical products. The Act also created a research exemption, indicating that "it shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention . . . solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products." 35 U.S.C. § 271(e)(1) ("Bolar exemption"). This provision overturned the Federal Circuit decision in Roche Products, Inc. v. Bolar Pharmaceutical Co., Inc., 733 F.2d 858 (1984), which held that the traditional experimental use exemption to patent infringement (35 U.S.C. § 271(a)) did not apply to pre-market testing done by a generic manufacturer and submitted to a regulatory agency. [….]. Notwithstanding the EU Directive, the exact language, scope and interpretation of Bolar exemptions vary across Europe. (Tridico 2014, 17--20)

The national laws on "Regulatory Data Exclusivity" protects the information of the initial authorization of the reference medicinal product for 10 to 11 years in Germany, Italy, Lithuania, Spain and UK (CMS Legal Services EEIG 2007).The Regulatory Data Exclusivity (RDE) right[84] is independent of other IP rights (such as patent or trade secret). Hence, this RDE right shall be protected for that tenure (10-11 years) independent of the term of patent. If this RDE goes parallel with the patent, then patent lasts longer and RDE exhausts within the term of protection of the patent. But if the patented invention is delayed to enter the market as product, this RDE can extend the life of the IP protection of that original invention. Data Exclusivity Right (DER) exist in the US and the EU to offer protection in varying length. Section 355 of the US Federal Food, Drug, and Cosmetic Act[85] provides provision for the protection of similar/same right. Article 39 of the TRIPS Agreement, which calls for protection against unfair competition,[86] is interpreted by the US and EU to extend the

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[81] Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community Code Relating to Medicinal Products for Human Use, 2004 O.J. (L 136) 34, 39.
[82] *Id*. art. 10(5).
[83] *Id.* art. 10(6).
[84] Judit Rius Sanjuan explained: "The terms "marketing exclusivity," "market exclusivity," "new drug product exclusivity," "Hatch-Waxman exclusivity," "sui generic protection," "data exclusivity," and "data protection" are all found in the U.S. and/or E.U. legal literature. Usually the term "marketing exclusivity" is more used in the U.S. regulatory system, and both the terms "data protection" and "data exclusivity" are more used in the E.U. system." (2006, 2n5).
[85] 21 U.S.C.§ 355 (2010). http://www.gpo.gov/fdsys/pkg/USCODE-2010-title21/html/USCODE-2010-title21-chap9-subchapV-partA-sec355.htm.
[86] Art. 39 (3) TRIPS Agreement states: "Members, when requiring, as a condition of approving the marketing of pharmaceutical […] products which utilize new chemical entities, the submission of undisclosed test or other data, the origination of which involves a considerable effort, shall protect such data against unfair commercial use. In addition,

DER in favor of the IP right owner potentially delaying the chance of the generic entering the market Moreover, the exercise of compulsory licensing have to take into account the "patent and the data exclusivity right" both. Much stronger IP protection exist in the US and EU than the TRIPS required for the protection of pharmaceutical test data. Judit Rius Sanjuan made the following criticism of offering strong DER:

> The granting of exclusive rights in test data will delay the entry of generic products into the market, impeding the access to affordable medicines. [….]. The exportation of the U.S. Hatch-Waxman regime to other countries with very different income and needs has been strongly criticized by one of its proponents, Representative Henry A. Waxman.
>
> It is a form of double protection, since the strong patent rights are justified by the cost of investments in test data. According to this line of thinking, stronger rights in the data should be offset by weaker protections for the patent. […]
>
> Unless the exclusive rights in the data can be overridden, it can make compulsory licenses of patents or government use orders ineffective.
>
> It undermines the Bolar/ Early Working patent exception which seek to encourage quick access to the post patent market for generic medicines by exempting from patent liability certain conducts. (Sanjuan 2006, 16; footnote omitted)

When the double protection of patent and DER are offered to the Biotech companies for the "stem cell based invention" and the test data of "stem cell based therapies," the IP protection may substantially delay the generic manufacturer entering into market. Bolar exemption will not do much to increase the access to the therapy. Stem cell patents raises other concerns too. Granting broad patent in emerging techniques of biomedical science creates the fear of blocking the downstream research. Because the upstream inventions having no direct application for therapeutic purpose, might be essential for downstream research for drug development. They form the "essential facility" for further innovation (for example, WARF patents on ES cell derivation) (McCoy 2008-2009, 86). The competition law and the compulsory licensing regime may not be enough tool to break the power of monopoly.

The respondents were asked (question no. 8): "How many years of protection (term of protection for commercial exploitation) is appropriate for human stem cell based inventions/innovations?". The following *Major Key Themes* derived from the responses to question no. 8 shows that a few of them made comments and they supported 20 years or more for the IP protection of hSCI:

- "Regulatory approvals";
- Current protection;
- 20 or more than 20 years is appropriate;

Members shall protect such data against disclosure, except where necessary to protect the public, or unless steps are taken to ensure that the data are protected against unfair commercial use." TRIPS Agreement art. 39.

The interpretation of the *Major Key Themes* derived from responses to question no. 8 can be found in ch. 5.

4.4.3 CONTROVERSIES, SLIM DIFFERENCES AMONG INVENTIONS, FUTURE LEGAL COMPLICATIONS

The Korean scientist Woo Suk Hwang was proclaimed as "the first to create a human embryonic stem cell line through cloning" (Ryan Davis, Law360, February 19, 2014) in 2004. Hwang et al. published the article "Evidence of a Pluripotent Human Embryonic Stem Cell Line Derived from a Cloned Blastocyst" in the journal *Science*[87] in 2004. But the journal retracted this publication and the subsequent *Science* publication[88] of the authors in 2006 after the Seoul National University (SNU) declared that the publications contained fabricated data (Kennedy 2006). The scientist Woo Suk Hwang[89] was issued the United States Patent No. 8,647,872 on February 11, 2014[90] for "[h]uman embryonic stem cell line prepared by nuclear transfer of a human somatic cell into an enucleated human oocyte."[91] As the retracted publication and patented inventions are claimed to be either same or similar by some commentators,[92] several comments and criticisms surfaced after the issuance of this patent. What can be possible impacts of such patents? Either the patent is meaningless (as the invention cannot be implemented) or it may form the part of *prior art* for the invention of Shoukhrat Mitalipov who claimed to have successfully cloned human embryo by SCNT and derived human embryonic stem cells by SCNT in 2013 (Tachibana et al. 2013).[93] From the patent perspective, the United States Patent No. 8,647,872 is the first of its kind, but the authenticity of the invention was questioned and the patent claim was also broad (Jeanne Loring, Knoepfler Lab Stem Cell Blog, Feb. 12, 2014). Either it encompasses fake protocol or may form prior art for the invention of Tachibana et al (2013). Irrespective of the fact that Woo Suk Hwang's inventions were claimed to be fabricated, the US Patent and Trademark Office (USPTO) issued the patent on the same or similar claims. It appears that they (USPTO) do not possess the capacity or resources of "replicating" the invention to see if the claim truly embodies/produces an invention. This is a vital weakness in the patent granting process for the new inventions in life sciences. As stem cell based inventions are emerging

[87] 303 SCIENCE 1669, 1669-74 (2004), doi:10.1126/science.1094515. The article was retracted by Science on January 20, 2006.

[88] The article by Woo Suk Hwang et al. titled "Patient-Specific Embryonic Stem Cells Derived from Human SCNT Blastocysts" was published in Science on 17 June 2005 (Vol. 308, No. 5729, pp. 1777-1783, doi:10.1126/science.1112286) was later (Jan. 20, 2006) retracted.

[89] Woo-Suk Hwang is one of the inventors (US Patent No. 8,647,872, issued on February 11, 2014).

[90] 8 years after the publications/papers were retracted.

[91] United States Patent and Trademark Office, *USPTO Patent Full-Text and Image Database, available at* http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=%2Fnetahtml%2FPTO%2Fsrchnum.htm&r=1&f=G&l=50&s1=8,647,872.PN.&OS=PN/8,647,872&RS=PN/8,647,872 (last visited Dec. 30, 2014).

[92] Andrew Pollack reported: "A committee at Seoul National University, where Dr. Hwang worked, concluded in 2006 that evidence in his papers was faked. Science retracted both papers […]. The patent, No. 8,647,872, […], covers a human embryonic cell line derived through cloning and the methods for creating that line. It appears to be the cell line that was the subject of the first Science paper." (The New York Times, Feb. 14, 2014).

Ryan Davis wrote: "Attorneys say that while it is not clear that Hwang's U.S. patent is based on exactly the same research that led to his problems in Korea, it appears largely similar. U.S. Patent Number 8,647,872, issued Feb. 11, covers an embryonic stem cell line derived through cloning and the method for creating it." (Law360, February 19, 2014).

[93] However, Shoukhrat M. Mitalipov is one of the *inventors* (Shoukhrat M. Mitalipov, Don P. Wolf and James Byrne (inventors)) of the United States Patent No. 7,972,849 issued on July 5, 2011 for "[p]rimate pluripotent stem cells produced by somatic cell nuclear transfer" having the Oregon Health & Science University (Portland, OR) as the *assignee* of the patent. This patent (United States Patent No. 7,972,849) is also the prior art for the publication of Tachibana et al. (2013) which is the publication of the Mitalipov's team regarding an optimized procedure of the SCNT technology for human embryo cloning and extracting the cells from the cloned embryo. But 2013's publication (Tachibana et al. (2013) by the team of Mitalipov) has not been issued US patent yet.

technology in the discipline of life science, there are more legal complications going to arise due to fake or bad patents. Those patents (fake or bad ones) may create hurdle to do research and get the patent for the credible inventions that take place subsequent to them. Filing a case/petition to declare the patent unenforceable (or apply for revocation/opposition/reexamination procedure) is also another extra burden on who might be making an invention that may apparently infringe a fake or bad patent. The following diagram illustrates the complications arising from the above situation:

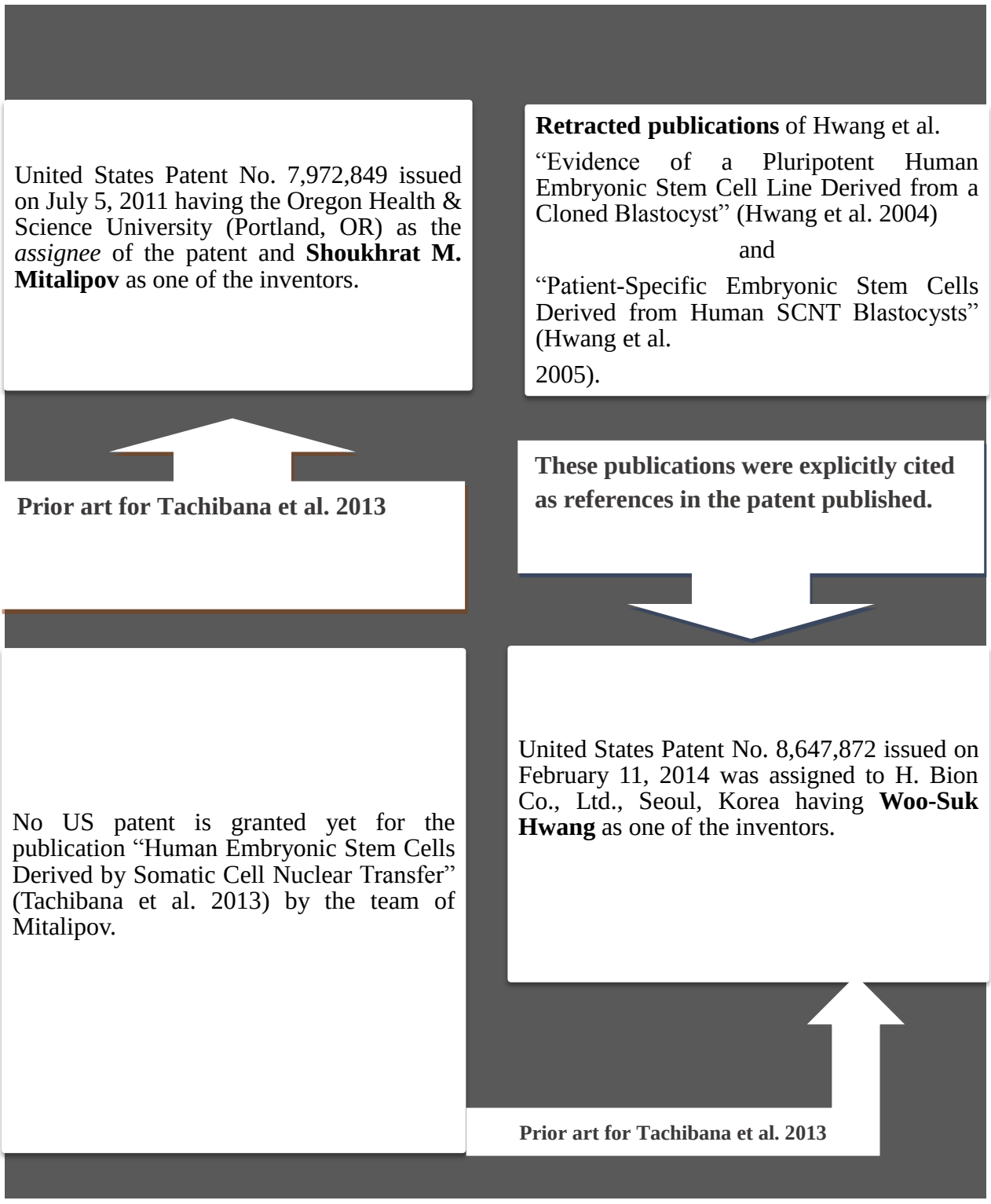

Fig. 4.4 They may have to experience reexamination / post-grant proceedings / patent litigation

Following diagram shows the yearly (in recent years) stages of development in the human stem cell based inventions.[94]

[94] For this diagram, I have chosen the SCNT and its neighboring techniques for producing *pluripotent* stem cells.

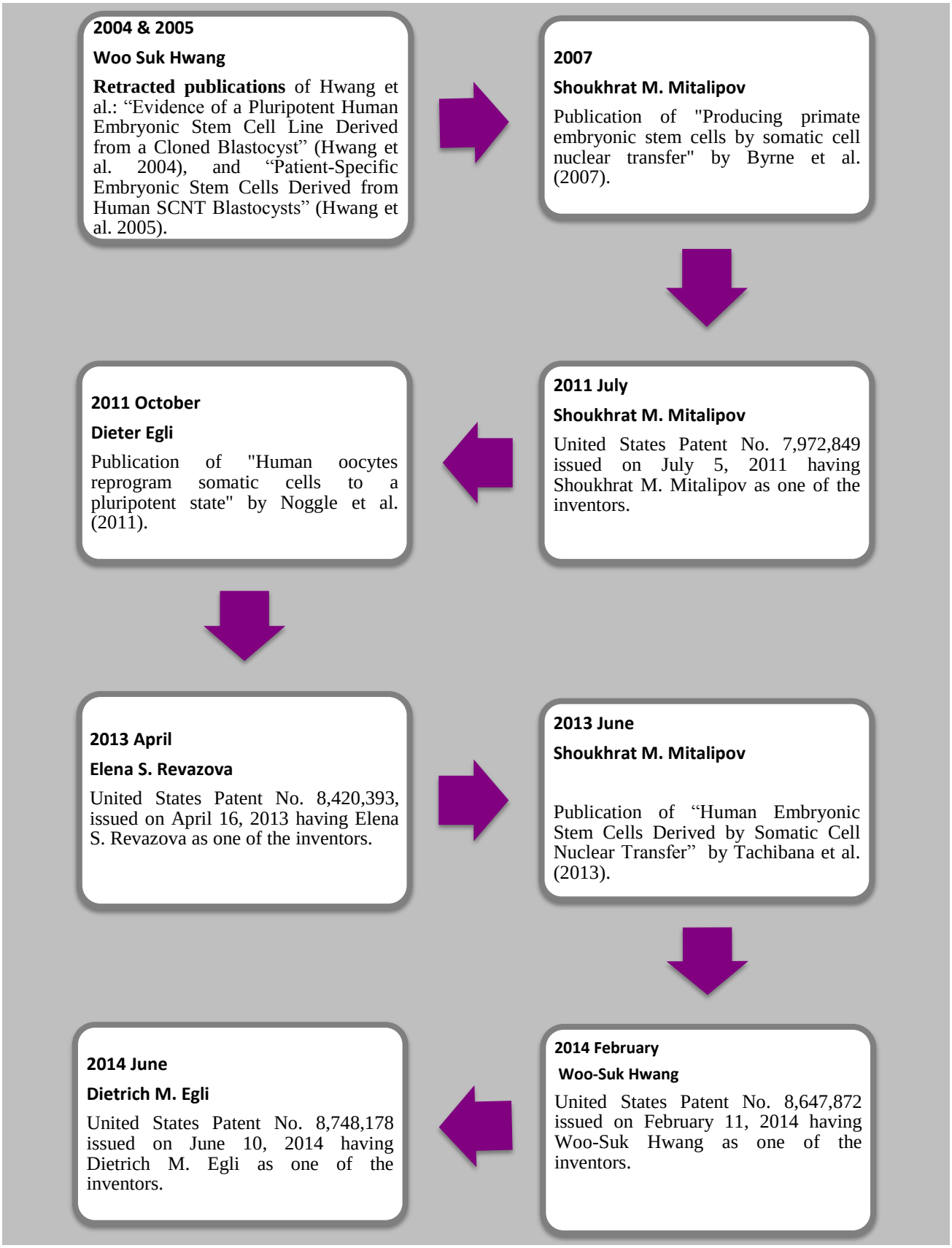

Fig. 4.5 The breakthrough publications, inventions and patents (U.S. Patents) in SCNT and its neighboring techniques from 2004 to 2014

In one case (Hwang et al. 2004; Hwang et al. 2005), the publications were retracted on the allegations of fabricated data but US patent[95] was issued having the references of those publications. Noggle et al. (2011) and Tachibana et al. (2013) both derived human *pluripotent* stem cells but with an important distinction involving/surrounding the "*oocyte nucleus removal* step." Noggle et al. (2011)[96] did not involve removal of oocyte nucleus prior to introduction of somatic cell nucleus. Tachibana et al. (2013),[97] on the other hand, used an optimized SCNT procedure that involved caffeine treatment during spindle removal (oocyte nucleus removal) to get rid of the problem that Noggle et al. (2011) mentioned earlier,[98] i.e., developmental failure at the early stage. The invention based on Noggle et al. (2011) was issued United States Patent No. 8,748,178 on June 10, 2014[99] but no patent is yet issued on the invention of Tachibana et al. (2013).

In 2013, the United States Patent No. 8,420,393 was issued for "[g]eneration of an autologous stem cell library from human oocytes parthenogenetically activated by high or low oxygen tension" and was assigned to International Stem Cell Corporation having Elena S. Revazova, Marina V. Pryzhkova, Leonid N. Kuzmichev and Jeffrey D. Janus as the inventors.[100] The 2004 research paper of Hwang et al. (2004) titled "Evidence of a Pluripotent Human Embryonic Stem Cell Line Derived from a Cloned Blastocyst" published in *Science* (later retracted in 2006) claimed to have made the SCNT-ES cells but left some ambiguity. The abstract of Hwang et al. (2004, 1669; retracted in 2006) stated that, "[a]lthough we cannot completely exclude the possibility that the cells had a parthenogenetic origin, imprinting analyses support a SCNT origin of the derived human ES cells." Although they claimed to have DNA imprints (DNA matching analysis) data supporting that it was indeed made by employing SCNT, they did not completely rule out that this invention might be due to parthenogenesis and not SCNT. In the subsequent article published in 2005 in *Science* (later retracted in 2006) by Hwang et al., there was, however, no room for ambiguity in their language. They (Hwang et al. 2005) further substantiated that the invention is the result of SCNT, not parthenogenesis, by presenting supporting DNA imprint and histocompatibility (matching with the patient who donated somatic cell nucleus) data. Hwang et al. (2005, 1777; retracted in 2006) stated in the abstract: "NT-hESCs were pluripotent, chromosomally normal, and matched the NT patient's

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[95] United States Patent No. 8,647,872, issued on February 11, 2014 was assigned to H. Bion Co., Ltd., Seoul, Korea having Woo-Suk Hwang as one of the inventors. United States Patent and Trademark Office, *USPTO Patent Full-Text and Image Database*, *available at* http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=%2Fnetahtml%2FPTO%2Fsrchnum.htm&r=1&f=G&l=50&s1=8,647,872.PN.&OS=PN/8,647,872&RS=PN/8,647,872 (last visited Nov. 7, 2014).

[96] The process by which the team of Dieter Egli made human *pluripotent* stem cells is not the standard procedure of Somatic Cell Nuclear Transfer (SCNT), in the strict sense. They skipped one important step of SCNT. In SCNT, the nucleus of the egg is removed and replaced with the donor nucleus. They (Noggle et al. 2011) did not remove the egg nucleus but inserted donor nucleus additionally. Noggle et al. (2011, 70) reported that, "if the oocyte genome is not removed and the somatic cell genome is merely added, the resultant triploid cells develop to the blastocyst stage. Stem cell lines derived from these blastocysts differentiate into cell types of all three germ layers[…]. This result demonstrates the feasibility of reprogramming human cells using oocytes […]."
The background of the invention of the U. S. Patent No. 8,748,178 states that, "[t]o date, no methods are known for the derivation of a human embryonic stem cell line after nuclear transfer, although nuclear transfer embryos have been generated which have developed to the cleavage stages." United States Patent No. 8,748,178, issued on June 10, 2014.

[97] Published in June 2013.

[98] Published in October 2011.

[99] United States Patent No. 8,748,178 was issued on June 10, 2014, assigned to the New York Stem Cell Foundation (New York, NY), having Dietrich M. Egli, Scott A. Noggle and Kevin C. Eggan as the inventors. United States Patent and Trademark Office, *USPTO Patent Full-Text and Image Database*, *available at* http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=%2Fnetahtml%2FPTO%2Fsrchnum.htm&r=1&f=G&l=50&s1=8,748,178.PN.&OS=PN/8,748,178&RS=PN/8,748,178 (last visited Nov. 7, 2014).

[100] U.S. Patent No. 8,420,393, issued on Apr. 16, 2013. United States Patent and Trademark Office, *USPTO Patent Full-Text and Image Database*, *available at* http://patft.uspto.gov/netacgi/nph-Parser?Sect2=PTO1&Sect2=HITOFF&p=1&u=/netahtml/PTO/search-bool.html&r=1&f=G&l=50&d=PALL&RefSrch=yes&Query=PN/8420393 (last visited Nov. 7, 2014).

DNA. The major histocompatibility complex identity of each NT-hESC when compared to the patient's own showed immunological compatibility, which is important for eventual transplantation." The United States Patent No. 8,647,872 assigned to H. Bion Co., Ltd., Seoul, Korea having Woo-Suk Hwang as one of the inventors, was clearly directed towards preparation of embryonic stem cell lines by SCNT, not indicating the issue of parthenogenetic origin of the cells (US Patent No. 8,647,872, issued on February 11, 2014).

In summary, the following important events need to be taken into account:

- Elena S. Revazova et al. was issued the patent in 2013 for the generation of cells parthenogenetically activated by high or low oxygen tension;
- Woo-Suk Hwang and others were issued the patent in 2014 on extraction of embryonic stem cell by SCNT, although their first paper (later retracted) made reference of parthenogenetic origin of the cells;
- No one has reported to have been successful in replicating the inventions claimed by Woo-Suk Hwang et al. (2004; 2005) and the *Science* retracted the papers after the Seoul National University (SNU) announced that the papers contained fabricated data (Kennedy 2006);
- The U.S. Patent 8,647,872 of 2014, Woo-Suk Hwang and others are awarded, is essentially the invention that Tachibana et al. (2013) successfully accomplished but they (Tachibana et al. (2013); the team of Shoukhrat M. Mitalipov) have not yet been awarded any U.S. patent.

In the recent past, there had been many incidents of reexamination and litigation against stem cell patents (Shyntum and Kalkreuter 2009). Many breakthrough patents are challenged or targeted at the patent offices or at Court, e.g.,

- WARF's US Patent No. 7,029,913 was challenged in *Consumer Watchdog v. Wisconsin Alumni Research Foundation*[101] at the United States Court of Appeal for the Federal Circuit and was unsuccessful;
- "Inter Partes Review" petition was filed against the Kyoto University by BioGatekeeper, Inc. for the US Patent No. 8,058,065 (issued on November 15, 2011, assigned to Kyoto University) at USPTO (Official Gazette of the United States Patent and Trademark Office, Sept. 16, 2014).

The complications in intellectual property protection through patent may slower the pace of the invention to reach the patient.

4.5 DIVERGENT PATENT FRAMEWORK FOR hSCI

The patent framework of hSCI is mainly divergent on the grounds of "*ordre public* and morality." The differences on the grounds of patentability requirements between Europe and the USA exists but they are not the main constraints on the *granting* and *rejection* of a human stem cell patent. Rather the interpretation of the "exclusion from patentability" on ethical grounds has created a difference in granting or rejecting a patent application.

4.5.1 THE PREVAILING CIRCUMSTANCES IN hSCR AND PATENT: HOW DIVERGENT

Samantha A. Jameson (2007, 197) made a comparison of patentability of biotechnological inventions in the EU and USA and commented: "For inventions dealing with humans and cells, there are divergent approaches as to whether and how research should be promoted or discouraged, but the ability to patent appears broader in the U.S., since patents may be available on embryonic stem cell

[101] Case 13-1377, Fed. Cir. 2013.

lines and cloning [therapeutic]." Daniel J. Kelves (2002, 60) commented that, "even though American patent law continues to be literally amoral, anyone seeking a patent on a living organism in Europe will have to satisfy the requirements of Article 53(a)." The vison and goals of the patent system in Europe and the USA are different. For the human subject protection in biomedical research, both Europe and the USA have differently set mechanisms. The USA considers (for patenting hSCI) the innovation and application aspect of the research outcome more, rather than concentrating on the intricacies of the research process. But in Europe, the use of base material and their research process may lead to exclusion of the invention from patenting in many of the countries. However, the UK seems to have pursued significantly different goals from the European community's direction in hSCR but similar to the USA.

Destruction of embryo (or its use in different ways for the derivation of stem cells) in hESC research does not bar patenting in the USA. In many States of the USA, IVF redundant embryos can be used for research and hESC based inventions can also be patented from the USPTO. The stem cell research atmosphere in the USA after the Executive Order of President Obama, 2009[102] is described by Arif Jamil:

> There is an environment more conducive to HSCR and patent in the United Sates than in Europe at this moment. […]. There is no federal law that completely bans or prohibits HSCR but the Dickey- Wicker Amendment, 1995 had put restriction on availability of Federal Funding for research encompassing destruction of embryo, which is recently interpreted by the Court in *Sherley v. Sebelius* to be not an embargo for granting Federal Funding for stem cell research that "utilize already derived" embryonic stem cells. […] HSCR using donated embryos can be conducted with NIH Grants provided that they have been approved by the NIH according to its guidelines. (2013b, 151, notes omitted)

ClinicalTrials.gov serving as a database and registry of the U.S. National Institutes of Health providing information on the clinical studies conducted all over the world involving human subjects/participants currently (at the time of writing) shows 179,458 studies conducted in all 50 states of the US and in 187 countries.[103] A search using the key words "human embryonic stem cell"[104] in that database of ClinicalTrials.gov shows 24 studies worldwide.[105] The map showing the geographical location of those 24 results reveal 8 studies in the US and three 3 in Europe.[106] The maps of the US and Europe showing the location[107] of the studies are following:

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[102] Executive Order 13505, Vol. 74, No. 46, Fed. Reg. 10667 (Mar. 11, 2009).

[103] *ClinicalTrials.gov*, U.S. NATIONAL INSTITUTES OF HEALTH (Nov. 27, 2014, 12.51 PM CET), http://clinicaltrials.gov/ct2/home.

[104] Human embryonic stem cell research attracts most of the ethical controversies.

[105] *ClinicalTrials.gov*, U.S. NATIONAL INSTITUTES OF HEALTH (Nov. 26, 2014, 10.54 AM CET), http://clinicaltrials.gov/ct2/results?term=human+embryonic+stem+cell+&Search=Search.

[106] But the detailed map of the Europe shows only two (2) studies; one in the UK and one in France. *ClinicalTrials.gov*, U.S. NATIONAL INSTITUTES OF HEALTH (Nov. 27, 2014, 13.17 PM CET), http://clinicaltrials.gov/ct2/results/map?term=human+embryonic+stem+cell.

[107] Some studies are showing multiple locations and appear in the maps of the regions concurrently wherever they are being conducted. *ClinicalTrials.gov*, U.S. NATIONAL INSTITUTES OF HEALTH (Nov. 27, 2014, 13.24 PM CET), http://clinicaltrials.gov/ct2/results/map/click?map.x=199&map.y=148&term=human+embryonic+stem+cell&map=NA%3AUS.

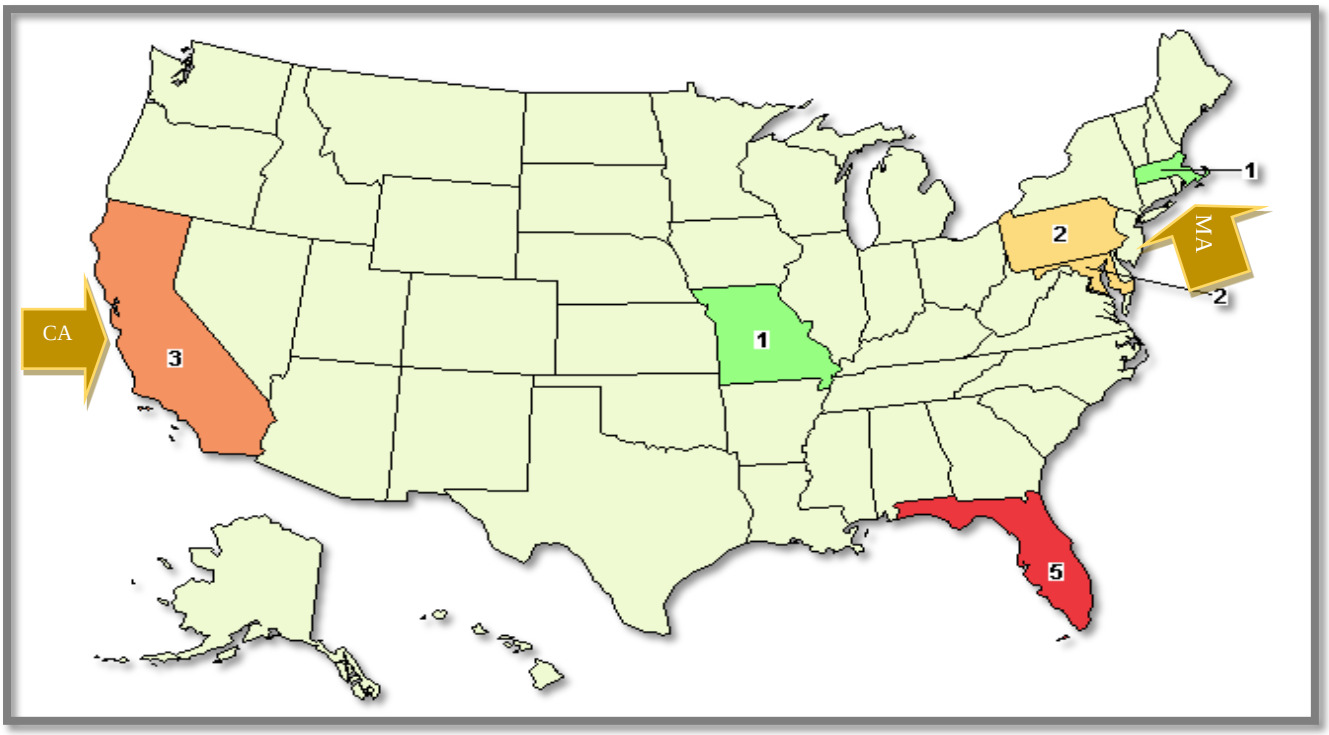

Fig. 4.6 Clinical trials related to "human embryonic stem cells" in the USA: Among others, three (3) studies taking place in California (CA) and one (1) in Massachusetts (MA) (Illustration from ClinicalTrials.gov: On a Map 2014; arrow (CA & MA) added by Arif Jamil)[108]

[108] Map of 24 studies found by search of human embryonic stem cell. *ClinicalTrials.gov*, U.S. NATIONAL INSTITUTES OF HEALTH (Nov. 27, 2014, 13.31 PM CET), http://clinicaltrials.gov/ct2/results/map/click?map.x=199&map.y=148&term=human+embryonic+stem+cell&map=NA%3AUS.

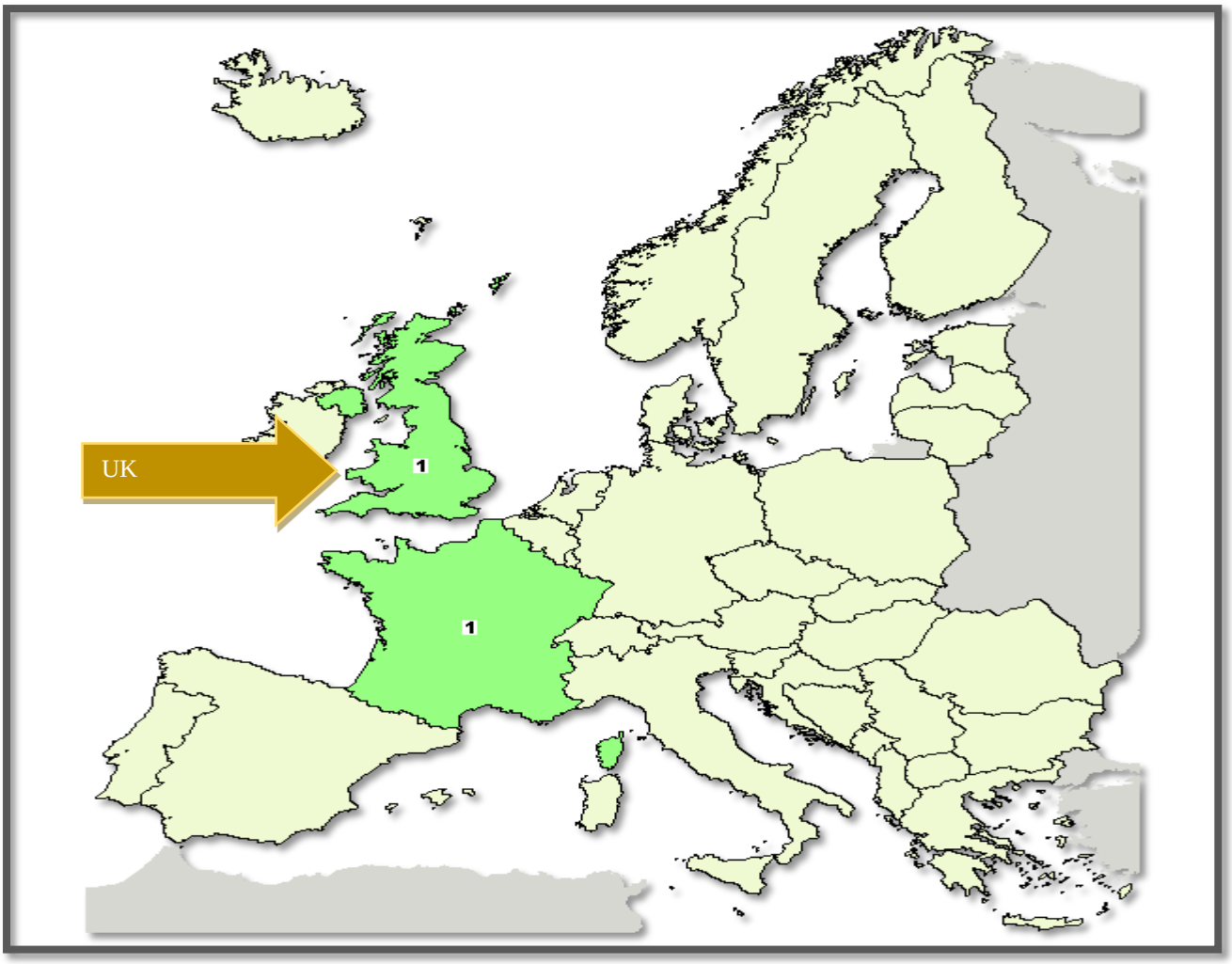

Fig. 4.7 Clinical trials related to "human embryonic stem cells" in the Europe: Among others, one (1) study is taking place in the UK. (Illustration from ClinicalTrials.gov: On a Map 2014; arrow (UK) added by Arif Jamil)[109]

The distribution of the studies (clinical trials) in the above geographical locations indicates that:

- research policies on human embryonic stem cells, clinical trials and patenting may have a connection;
- California and Massachusetts have liberal stem cell research policies and clinical trials are taking place in those States as well;
- US provides patent on hESC based inventions and so the highest number of studies are taking place in the US;[110]
- There is restriction on hESC research in many countries of Europe and the most liberal policies on stem cell research is prevalent in the UK. Hence, clinical trial of ESC based

[109] Map of 24 studies found by search of human embryonic stem cell. *ClinicalTrials.gov*, U.S. NATIONAL INSTITUTES OF HEALTH (Nov. 27, 2014, 14.06 PM CET), http://clinicaltrials.gov/ct2/results/map?term=human+embryonic+stem+cell&map=EU.

[110] A number of 8 out of total 24 studies (clinical trial) are conducted in the USA. *ClinicalTrials.gov*, U.S. NATIONAL INSTITUTES OF HEALTH (Nov. 27, 2014, 14.16 PM CET), http://clinicaltrials.gov/ct2/results/map?term=human+embryonic+stem+cell&map.

invention is also taking place in the UK. The study (titled as "Safety and Tolerability of Sub-retinal Transplantation of Human Embryonic Stem Cell Derived Retinal Pigmented Epithelial (hESC-RPE) Cells in Patients With Stargardt's Macular Dystrophy (SMD)") recruiting participants is sponsored by the Advanced Cell Technology, MA, USA and it is held at Moorefields Eye Hospital NHS Foundation Trust, London, UK.[111] The Advanced Cell Technology is pioneering the application/use of hESCs derived from blastomere cell of the pre-implantation stage embryo. It appears that, those studies are concentrated in countries that are not strict towards the stem cell research and hSCI's patent.

The use of egg for hSCI is not explicitly stated as contrary to the perception of "morality," when it comes to patenting. Therefore, the use of eggs for SCNT based inventions and parthenogenetic egg activation for stem cell research shall not bar the patenting in Europe or the USA. With the emergence of inventions/innovations, patents and applications (in degenerative conditions and diseases) of the SCNT and parthenogenetic stem cells, egg procurement may raise ethical concern in future. Until now, patent litigations have not found the use of human eggs for the stem cell research contrary to the notion of "morality." The justification, necessity and implications of egg donation on the health of the donor have not been associated with the "*ordre public* and/or morality" by any law yet. The patent restrictions (in Europe) on technique that derives ES by embryo destruction, probably has inspired to invent multiple techniques to bypass that step (destruction of embryo).

The CJEU in *Oliver Brüstle v.Greenpeace e.V.* (2011) while excluding the use of human embryo for the purpose of patenting from the scientific researches extended the definition of embryo to "any non-fertilised human ovum whose division and further development have been stimulated by parthenogenesis".[112] The Court of Justice of the European Union has taken a different stand in a subsequent case involving patentability of hSCs from parthenogenetically activated oocytes (eggs). In the case of *International Stem Cell Corporation*, (2014) the CJEU decided that the parthenogenetically activated oocytes (eggs) shall be excluded from the definition of the embryo in *Brüstle* case "if, in the light of current scientific knowledge, it [parthenote] does not, in itself, have the inherent capacity of developing into a human being".[113] Therefore, the capacity (potential) of the organism to develop into a human being was an ethical concern for the exclusion from patentability for the European Court. In the light of this decision, hpSCs are not excluded from patenting as European Patent. International Stem Cell Corporation, California currently holds the US patents on derivation of hpSCs.[114]

The iPSC patents are unlikely to be challenged on the ethical grounds, simply because from the research to the application it does not use any sensitive human biological material, e.g., egg and embryo. It uses only somatic cell and the reprogrammed cells shall go into application directly. While the ethical issues for iPSCs are different from other forms of hSCR, it will pass the test of

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[111] *ClinicalTrials.gov*, U.S. NATIONAL INSTITUTES OF HEALTH (Nov. 27, 2014, 14.37 PM CET), http://clinicaltrials.gov/ct2/show/study/NCT01469832?term=human+embryonic+stem+cell&cntry1=EU%3AGB&rank=1.

[112] C-34/10, Judgment of the Court (Grand Chamber) 18 Oct. 2011, paragraph 53, also *available at* http://curia.europa.eu/juris/document/document.jsf?text=&docid=111402&pageIndex=0&doclang=EN&mode=lst&dir=&occ=first&part=1&cid=90420 (last visited Dec. 22, 2014).

[113] Case C‑364/13, International Stem Cell Corporation v. Comptroller General of Patents, Designs and Trade Marks, Judgment of the Court (Grand Chamber) 18 Dec. 2014, paragraph 39, also *available at* http://curia.europa.eu/juris/document/document.jsf;jsessionid=9ea7d0f130de9c4121923b8f43769c42c1706a04f989.e34KaxiLc3eQc40LaxqMbN4ObheSe0?text=&docid=160936&pageIndex=0&doclang=EN&mode=lst&dir=&occ=first&part=1&cid=88991#Footnote* (last visited Dec. 22, 2014).

[114] U.S. Patent No. 8,420,393, issued on Apr. 16, 2013. United States Patent and Trademark Office, *USPTO Patent Full-Text and Image Database*, *available at* http://patft.uspto.gov/netacgi/nph-Parser?Sect2=PTO1&Sect2=HITOFF&p=1&u=/netahtml/PTO/search-bool.html&r=1&f=G&l=50&d=PALL&RefSrch=yes&Query=PN/8420393 (last visited Dec. 22, 2014).

patenting easily, even in European countries. US Patent on ESC from the pre-implantation stage blastomere cell has not yet raised the ethical issue for the derivation of *totipotent* cells.[115] Advanced Cell Technology, Inc. (Ocata Therapeutics, Inc), Marlborough, MA was assigned the United States Patent No. 8,742,200[116] for the "[d]erivation of embryonic stem cells and embryo-derived cells".[117] The claimed invention stated in the "summary of the invention" that, "[t]he ES cells produced from the blastomere may be pluripotent or by some definitions totipotent."[118] European Patent application number 12197502.3 has two corresponding publications (Publication Nos. EP 2 612 906 A2 and EP 2 612 906 A3) appearing on the database of the European Patent Register for the "[d]erivation of embryonic stem cells and embryo-derived cells" having Advanced Cell Technology, Inc. as the applicants.[119] The European Search Report of the publication number EP 2 612 906 A3 mentioned that several claims of this patent application (EP 12197502.3) do not comply with the requirement of the "unity of invention".[120] The search report did not make reference of derivation of the cells that are by some definition *totipotent* as a problematic situation for the claims in their (Search Division, European Patent Office) observation stating the lack of unity of invention.[121] However, the patent examination is pending.[122]

From the procedural perspective, following figure shows how multilayered the patent system in Europe is, in comparison with the same in the US:

[115] The *totipotent* cells, each has the total ability to form a complete organism.
[116] Issued on June 3, 2014.
[117] United States Patent and Trademark Office, *USPTO Patent Full-Text and Image Database*, *available at* http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO2&Sect2=HITOFF&p=1&u=%2Fnetahtml%2FPTO%2Fsearch-bool.html&r=1&f=G&l=50&co1=AND&d=PTXT&s1=8,742,200&OS=8,742,200&RS=8,742,200 (last visited Nov. 12, 2014).
[118] U.S. Patent Number 8,742,200 (issued June 3, 2014). United States Patent and Trademark Office, *USPTO Patent Full-Text and Image Database*, *available at* http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO2&Sect2=HITOFF&p=1&u=%2Fnetahtml%2FPTO%2Fsearch-bool.html&r=1&f=G&l=50&co1=AND&d=PTXT&s1=8,742,200&OS=8,742,200&RS=8,742,200 (last visited Nov. 12, 2014).
[119] Database last updated on Nov. 12, 2014. European Patent Office, *European Patent Register*, *available at* https://register.epo.org/application?number=EP12197502&tab=main (last visited Nov. 12, 2014).
[120] European Patent Office, *European Patent Register*, *available at* https://data.epo.org/publication-server/pdf-document?pn=2612906&ki=A3&cc=EP (last visited Nov. 12, 2014).
[121] *Ibid*.
[122] At the time of this writing.

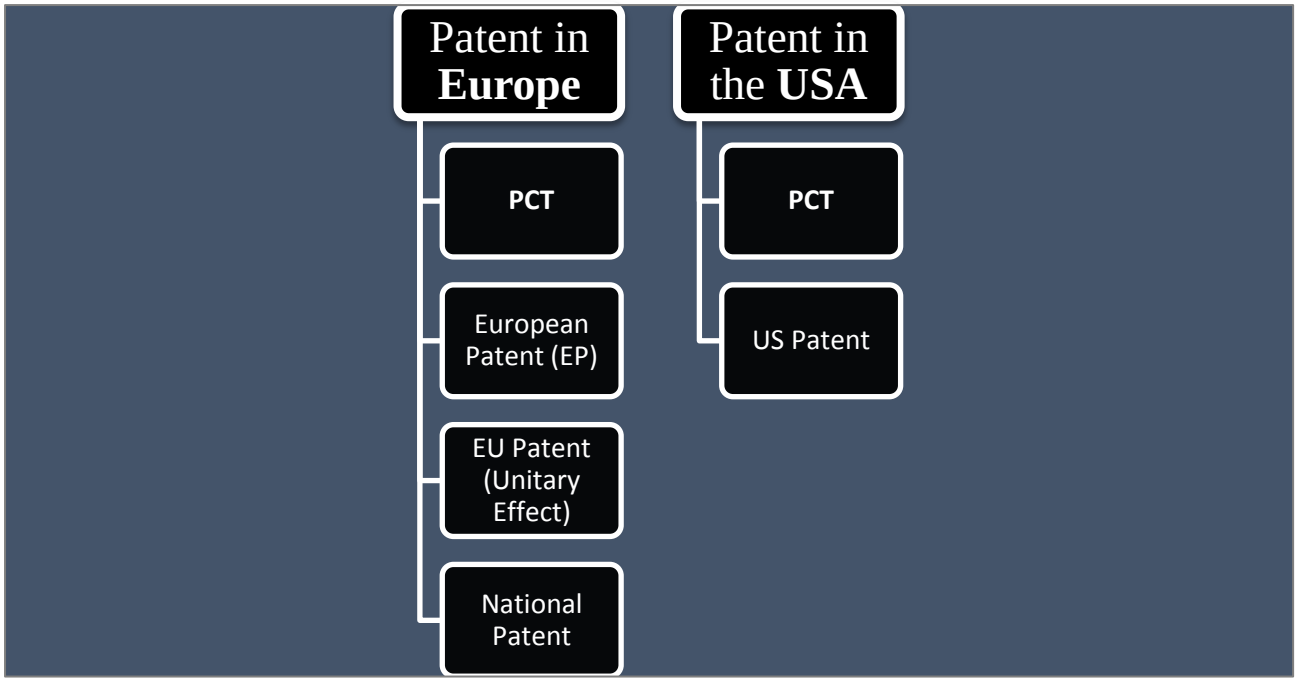

Fig. 4.8 Patenting Options and Routes in Europe and the USA

4.5.2 PATENT OFFICES (EPO, USPTO) AND FEES DIVERGENCE

Absolute divergence exist in the patent fees (grant and renewal).[123] Gaetan de Rassenfosse and Bruno van Pottelsberghe de la Potterie investigated the fee structure of 30 patent offices and found absolute divergences and variations when the fee is viewed and compared with "GDP per capita", "per million inhabitants" and the total amount of fees (2013, 700--702). Rassenfosse and Potterie reported from their analysis of fees of "30 patent offices worldwide": "[S]trong variations in the level of fees both over time and across countries suggest that there is no consensus regarding patent fees. This is also reflected in the high heterogeneity in fee schedules across countries, although it seems that fees generally rise with patent age." (Rassenfosse and Potterie 2013, 703). This is probably one of the reasons and justifications for differentiated pricing of patented goods. The assignee will not incur the same expenses for getting and maintaining the patent in all the jurisdictions. The patent will also not make the same profit from all the territories. Some countries may have smaller population but the number of consumers having the affordability of the product may be higher. Some countries might be large with huge population but the number of population possessing the affordability of that product may be low. The assignee will be keen to see how much profit the patent might be able to make from a market (population with affordability) after bearing the cost of the patent in that territory.

The EPO and US patent office functions in different styles and have different goals. The economic advantages associated to patent being more important in the US, the patentable subject matter is also relatively wider in range at the USPTO. At the EPO, *ordere public* and/or morality provision of EPC has narrowed the range of the patentable subject matter, e.g., the process patent on derivation of human ES cells by the destruction of human embryo is excluded at EPO.[124] The patentability criteria

[123] Patent fees may include fees (all or most of them) for filing/application, examination, grant, renewal, translation and validation (Rassenfosse and Potterie 2013, 715).

[124] The Enlarged Board of Appeal at EPO declared WARF's US patents on ES cell derivation are not patentable as European patent on November 25, 2008. Case No. G 0002/06. European Patent Office, *Search in the board of appeal decisions database, available at* http://www.epo.org/law-practice/case-law-appeals/recent/g060002ep1.html#q (last visited Dec. 11, 2014).

and the cost associated to the patent grant varies between the two offices (Mejer and Potterie 2011, 124--25). There is a continuously existing delay in the patent granting process of both the offices. The approximate time will be spent from the application to the grant at the EPO can be 44 months and at the USPTO 35 months (Mejer and Potterie 2011, 124). The number of patent application filed at USPTO is also higher than the EPO (Mejer and Potterie 2011, 122--23). Mejer and Potterie reported that the patent application filed in 2008 at EPO was 227,000, and 450,000 at the USPTO (2011, 122). Deepak Hegde (2012, 149) reported that, "patent applications at the USPTO have surged from 178,000 in 1991 to 509,000 in 2010." The higher number of patent applications does not necessarily testify that inventions have surged; it may also indicate that the number of bad patents are increasing. And if so, there will be increase in the post-grant proceedings and patent litigations. Deepak Hegde reported that, "the number of notices for lawsuits filed in selected US courts (US District Courts and US Courts of Appeals)" in the year 1993 was 1,047 and in 2009 it was 6,111 (2012, 5, Supplementary Table 5). Michele Boldrin and David K. Levine (2013, 3) commented that, "in spite of the enormous increase in the number of patents and in the strength of their legal protection, the US economy has seen neither a dramatic acceleration in the rate of technological progress nor a major increase in the levels of research and development expenditure."

Patent fees varies between the patent offices. The EPO and USPTO have different fees for search, examination, grant and renewal (Rassenfosse and Potterie 2012, 61).

UP will lower the patenting cost in the EU. No evidence from any empirical investigation was found that shows that higher fees means better quality of patents; but it is quite evident that lower fees means higher number of patents (Rassenfosse and Potterie 2012). Patents that are not eligible for EP or UP may try national patent (NP). National patents have lower value than a EP or US patent. Christine Greenhalgh and Mark Rogers found that, "on average, firms that receive only UK patents tend to have no significant market premium. In direct contrast, patenting through the European Patent Office does raise market value" (2006, 562). Gaetan de Rassenfosse and Bruno van Pottelsberghe de la Potterie observed that, "TRIADIC patents"[125] have higher quality and value (2009, 782--83). The patent offices around the globe evaluate the patent applications differently, work in different bureaucratic procedures and have different fee structures effective for markets of different type and size. Therefore, patent issued by different patent offices carry different meanings to the patent seekers. Aurora Plomer observed: "there is mounting evidence of significant variances in the evaluation of prior art and interpretation of patent standards across major patent offices around the world." (2010, 8; footnote omitted).

4.5.3 TERRITORIALITY OF PATENT SYSTEM AND THE ENFORCEMENT ISSUES

Article 4bis(1) of the Paris Convention for the Protection of Industrial Property, 1883 states that, "[p]atents applied for in the various countries of the Union by nationals of countries of the Union shall be independent of patents obtained for the same invention in other countries, whether members of the Union or not."[126] Article 16(4) of the Convention on Jurisdiction and the Enforcement of Judgments in Civil and Commercial Matters, 1968 states:

> The following courts shall have exclusive jurisdiction, regardless of domicile: [….] in proceedings concerned with the registration or validity of *patents*, trade marks, designs, or other similar rights required to be deposited or registered, the *courts of the Contracting State in which the deposit or registration has been applied for*, has

[125] Patents that are filed simultaneously at US Patent and Trademark Office (USPTO), European Patent Office (EPO) and Japan Patent Office (JPO) (Rassenfosse and Potterie 2009, 789).

[126] Paris Convention for the Protection of Industrial Property, Mar. 20, 1883, *available at* http://www.wipo.int/treaties/en/text.jsp?file_id=288514#P113_13775 (last visited Dec. 15, 2014).

> taken place or is under the terms of an international convention deemed to have taken place; [Italics added][127]

Article 24 of the Regulation (EU) No 1215/2012 of the European Parliament and of the Council of 12 December 2012 on Jurisdiction and the Recognition and Enforcement of Judgments in Civil and Commercial Matters (recast) mentioned:

> The following courts of a Member State shall have exclusive jurisdiction, regardless of the domicile of the parties: [….]
>
> (4) in proceedings concerned with the registration or validity of *patents*, trade marks, designs, or other similar rights required to be deposited or registered, irrespective of whether the issue is raised by way of an action or as a defence, the *courts of the Member State in which the deposit or registration has been applied for*, has taken place or is under the terms of an instrument of the Union or an international convention deemed to have taken place.
>
> Without prejudice to the jurisdiction of the European Patent Office under the Convention on the Grant of European Patents, signed at Munich on 5 October 1973, the *courts of each Member State shall have exclusive jurisdiction in proceedings concerned with the registration or validity of any European patent granted for that Member State*;
>
> (5) in proceedings concerned with the enforcement of judgments, the *courts of the Member State in which the judgment has been or is to be enforced*. [128] [Italics added]

All of these conventions recognize the territoriality of the patent system and acknowledge the right of the State to grant, reject and enforce a patent. Countries having the tendency of making unique interpretation of their "*ordre public* and/or morality" provision in the light of their self-perception on "ethical issues" regarding the hSCR policies will continue to apply the patent law differently from each other for the hSCI. Article 45(1)(a) of the Regulation (EU) No 1215/2012 of the European Parliament and of the Council of 12 December 2012 on Jurisdiction and the Recognition and Enforcement of Judgments in Civil and Commercial Matters (recast) gives authority to the State to reject enforcement of a judgment contrary to its notion of "*ordre public*".[129]

Article 64(3) of the European Patent Convention 1973 says that, "[a]ny infringement of a European patent shall be dealt with by national law."[130] The countries that will participate in the agreement for the Unified Patent Court (UPC) have consented to have "[a] Unified Patent Court for the settlement of disputes relating to European patents and European patents with unitary effect".[131] The Unified Patent Court (UPC) will substitute the need of approaching to the national court for the participating

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[127] Convention on Jurisdiction and the Enforcement of Judgments in Civil and Commercial Matters, 27 Sept. 1968, *available at* http://curia.europa.eu/common/recdoc/convention/en/c-textes/brux-idx.htm (last visited Dec. 15, 2014).
[128] 2012 O.J. (L 351) 1, 11.
[129] Article 45(1)(a) states that, "recognition of a judgment" can be rejected, "if such recognition is manifestly contrary to public policy (ordre public) in the Member State addressed". Regulation (EU) No 1215/2012 of the European Parliament and of the Council of 12 December 2012 on Jurisdiction and the Recognition and Enforcement of Judgments in Civil and Commercial Matters (recast) art. 45(1)(a), 2012 O.J. (L 351) 1, 15.
[130] *Supra* note 26.
[131] Agreement on a Unified Patent Court Art. 1, Feb. 19, 2013, 2013 O.J. (C 175) 1, 2.

States of the Agreement. Article 1 states: "The Unified Patent Court shall be a court common to the Contracting Member States and thus subject to the same obligations under Union law as any national court of the Contracting Member States."[132] But the European countries not taking part in the UPC shall retain the authority of their national courts for the litigations on patent enforcement and infringement.

The unitary patent package has also retained the national authorities over some of the issues that can affect the patent right of the applicant. Regarding the compulsory licensing, clause 10 of the preamble to the Regulation (EU) No 1257/2012 of the European Parliament and of the Council of 17 December 2012 Implementing Enhanced Cooperation in the Area of the Creation of Unitary Patent Protection states: "Compulsory licenses for European patents with unitary effect should be governed by the laws of the participating Member States as regards their respective territories."[133] The implication of this recognition of national jurisdiction is that if there were any differing approach of the national laws in licensing, it would remain to be so. There is no mechanism to enforce patent rights internationally. Patent remains at the hands of the individual States and has to be enforced by their judicial systems. However, once coming into effect, the UPC will be able to enforce patent (validity and infringement) with unitary effect in the contracting States altogether.

The issues of recognition and enforcement of foreign judgments is an important relevant topic for this discussion. Individual States follow their own laws and policies on how and to what extent recognize and enforce the foreign judgments. Countries pursue different approaches while implementing the policies and doctrines of private international laws. Principles of both public and private international laws can come into play when it comes to enforcement of IPR. Patent's validity and infringement is subject to interpretation by the adjudicating Court. Countries may also exercise restraint for the "Act of State" doctrine and prefer not to interfere with decision of other States. US Courts may not extend jurisdiction over foreign patents. The United States Court of Appeals for the Federal Circuit in *Voda v. Cordis Corp*.[134] decided that, "the district court had erred in granting supplemental subject matter jurisdiction under 28 U.S.C. § 1367 over foreign patent infringement claims" (Herzfeld 2007). Since the judicial system of individual States will resolve the patents' validity and infringement, the repetition of proceedings shall continue to occur. This will be increasing the enforcement costs of the patent owner. These issues relating to "recognition and enforcement" of "foreign judgment" and "foreign IP rights" will not be resolved any time soon.

4.5.4 MULTILAYERED PATENT PROTECTION IN EUROPE: INCREASED DIVERGENCE WITHIN EUROPE

[132] *Id.*
[133] Dec. 17, 2012, 2012 O.J. (L 361) 1.
[134] No. 05-1238 (Fed. Cir. Feb. 1, 2007).

Europe has the following patent systems existing simultaneously:

Fig. 4.9 Patent Systems Co-existing in Europe (at the time of the writing)

The Preparatory Committee of the Unified Patent Court drew the following diagram in their brochure, "An Enhanced European Patent System", showing the available routes of patenting in Europe after the EU patent shall come into force (The Preparatory Committee 2014):

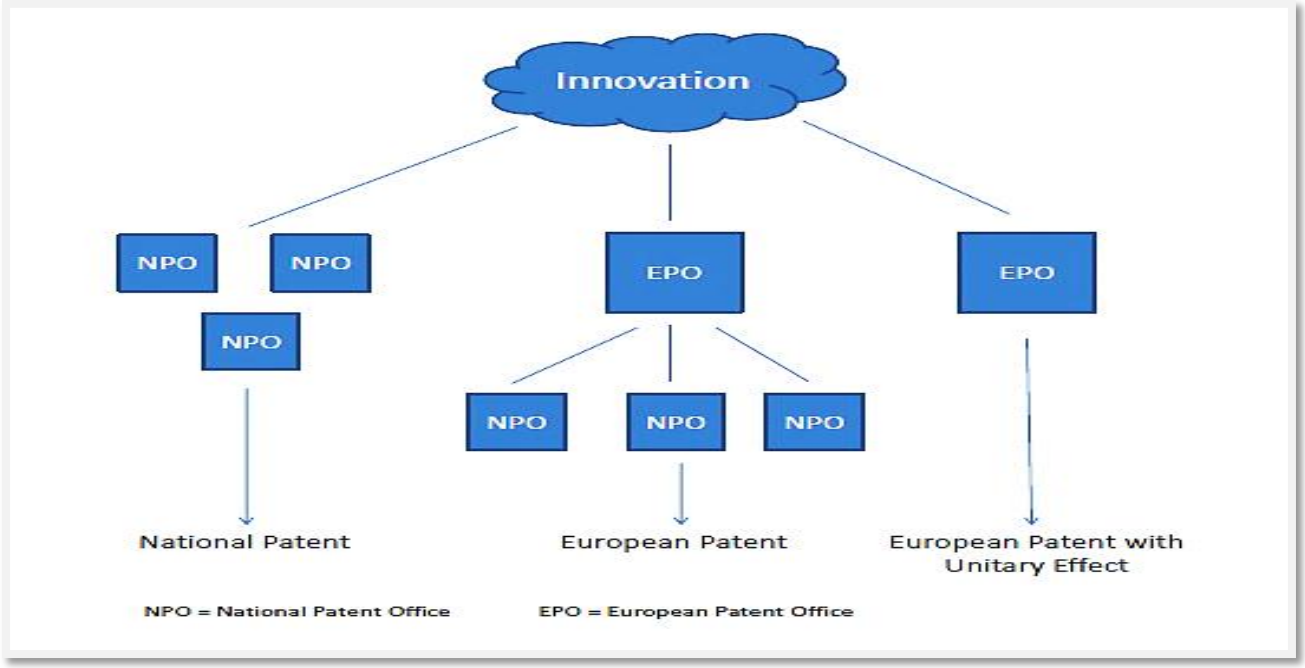

Fig. 4.10 Three Routes of Patent Protection in Europe (Illustration from the Preparatory Committee 2014, 3)

The European States have differing approaches in exercising the PCT route.

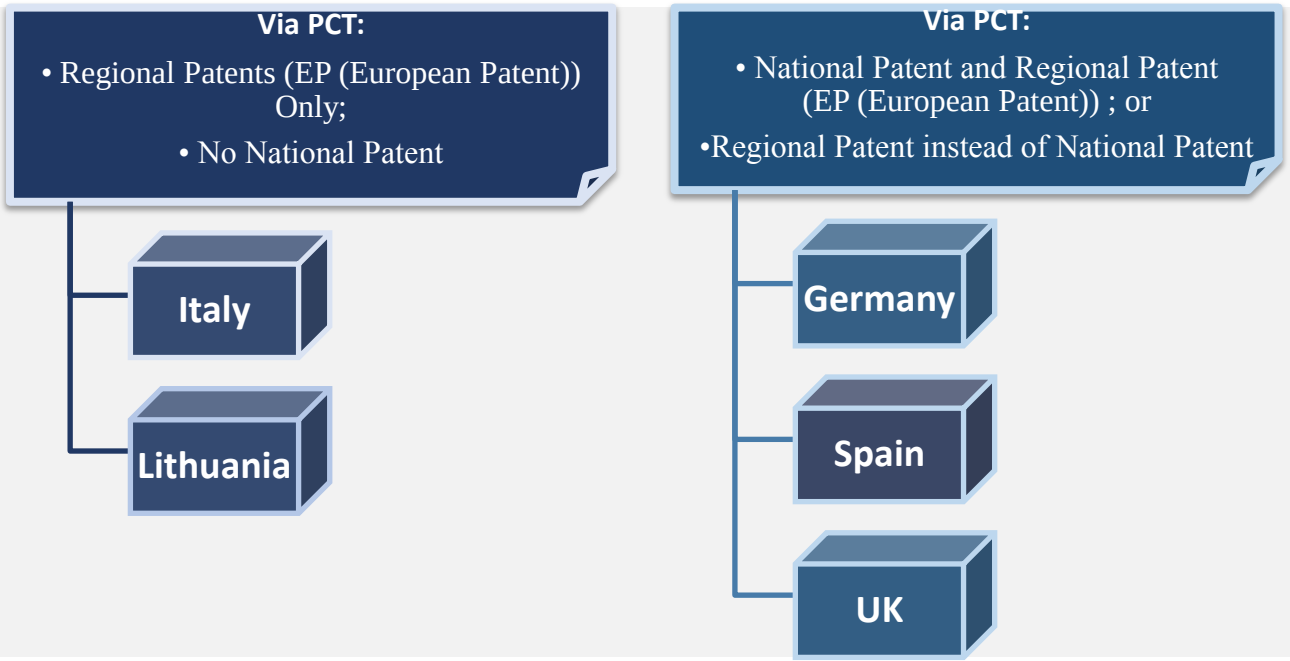

Fig. 4.11 Patent Route in Europe through PCT (WIPO: PCT Contracting States for which a Regional Patent can be Obtained via the PCT 2014)

4.5.4.1 EUROPEAN PATENT AND UNITARY PATENT PROTECTION

The Preparatory Committee of the Unified Patent Court in their brochure, "An Enhanced European Patent System", stated how the European Patent shall be given effect to Unitary Patent Protection

(The Preparatory Committee 2014) and the Steps are following:

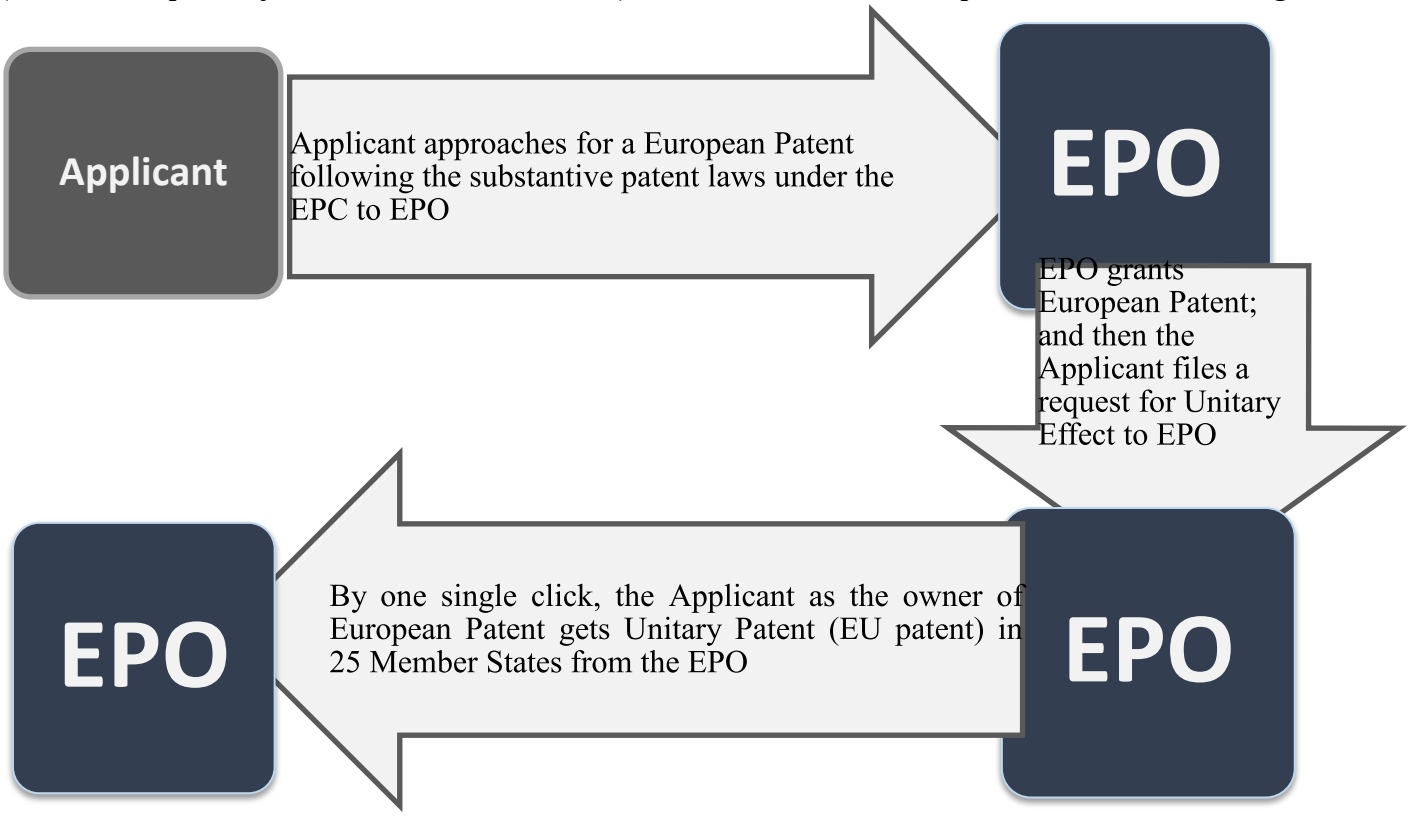

Fig. 4.12 Procedural Simplification. The applicant will get patents in 25 EU Member States by one single application (The Preparatory Committee 2014, 4--5)

The Unitary Patent (UP) protection will bring the following advantages for the patent owners:

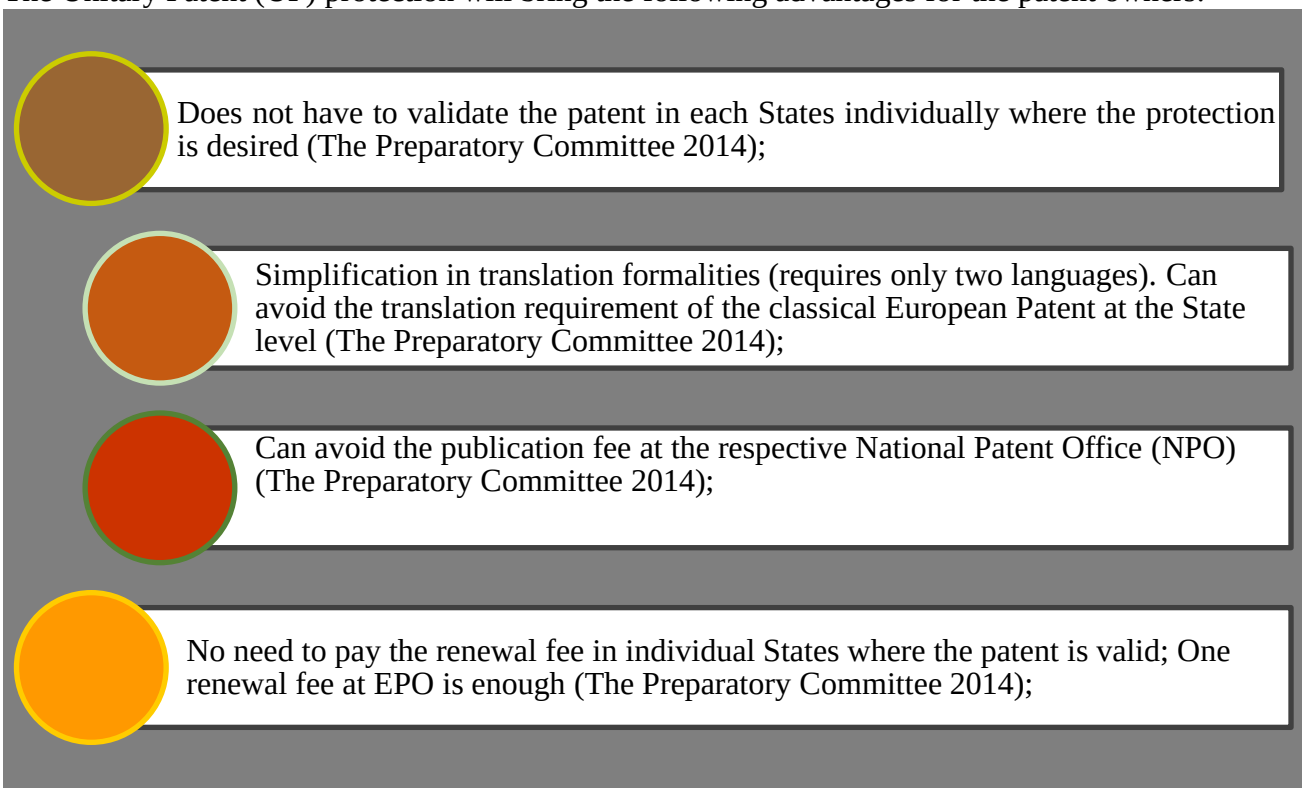

Fig. 4.13 The disadvantages EU Patent will overcome (The Preparatory Committee 2014, 5)

The areas addressed shall bring simplification in mainly the procedural and financial aspects of patenting in the EU Countries. This UP did not address any of the substantive concepts of patenting. The countries where the patenting of hSCI are subject to strict restrictions for embryo destruction or on ethical grounds, can not be taken to be a part of this cluster of patents. Hence, the patent seeker (prospective patentee) may have to try the classical European Patent's route and elect the individual States where the patent is obtainable. Therefore, for hSCI facing exclusion on ethical grounds in even one of the 25 States will not be able to get the Unitary Patent Protection; because the unitary effect is meant to be given in the 25 states en bloc. The authority of the States over granting a national patent remains at the hands of the States. So, the patents not qualified to give unitary effect, but eligible to get patent in any of the European State shall be enforced and challenged nationally. Therefore, the EU patent (Unitary Patent) and UPC will not do the harmonization of human stem cell patent landscape, particularly in the ethically contested inventions. According to the Article 64(3) of the European Patent Convention 1973, the infringement of a patent granted under the European Patent Convention "shall be dealt with by national law."[135] But a Unitary Patent shall be enforced and challenged at the Unitary Patent Court (hereinafter referred to as UPC). It is most likely that in *debated and controversial* areas of stem cell patents, EU patent will not be available and so the UPC will not be the forum of litigation for infringement and validity of such patents. Therefore, "the diversity in enforcement (infringement and validation) shall remain" in one hand, "the option of choosing the route of patenting shall increase" on the other hand, for those inventions. The ethically controversial inventions from the hSCR perhaps will find the "national patenting" as the better choice to explore.

[135] *Supra* note 26.

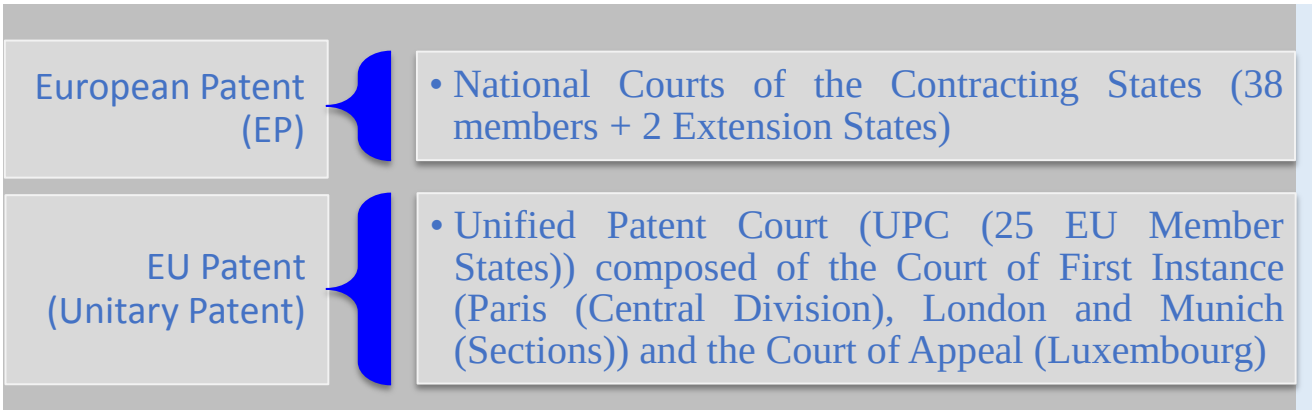

Fig. 4.14 Forum to address the validity and infringement of European and EU Patent (until the transitional period under the Agreement on a Unified Patent Court 2013 is over) (European Patent Office: Unified Patent Court 2014)

The jurisdiction of the UPC shall extend to:[136]

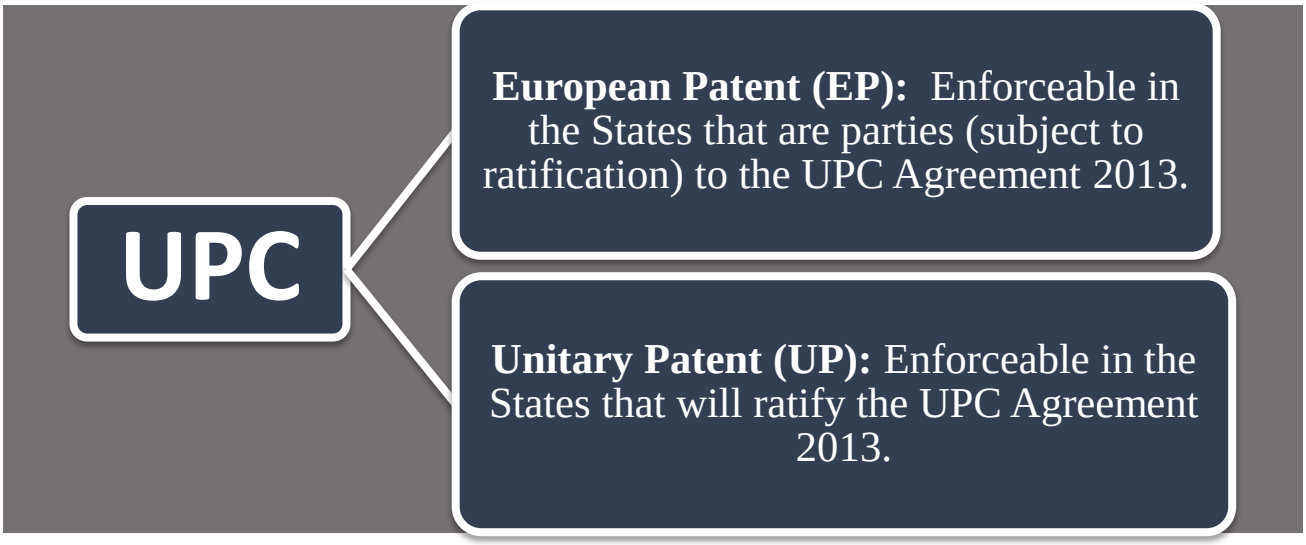

Fig. 4.15 The UPC will be competent to entertain disputes from the EP and UP and enforce the decision in the States ratifying the Agreement on a Unified Patent Court 2013

However, Article 83 of the Agreement on a Unified Patent Court 2013 (hereinafter referred to as UPC Agreement) provides a transitional period of 7 years (with the possibility of extension to a further 7 years) within which the actions can be brought to the national Court of the contracting States of the UPC Agreement on the infringement and revocation of a European Patent.[137]

[136] According to Article 34 of the Agreement on a Unified Patent Court 2013, the "[t]erritorial scope of decisions" of the UPC is stated as following: "Decisions of the Court shall cover, in the case of a European patent, the territory of those Contracting Member States for which the European patent has effect." Agreement on a Unified Patent Court, Feb 19, 2013, 2013 O.J. (C 175) 1.

[137] Article 83(1) stated that, "[d]uring a transitional period of seven years after the date of entry into force of this Agreement, an action for infringement or for revocation of a European patent or an action for infringement or for declaration of invalidity of a supplementary protection certificate issued for a product protected by a European patent may still be brought before national courts or other competent national authorities." *Id.*

An observation on the implications of the Unitary Patent package by Arif Jamil reveals how one of the major objectives of "cost reduction" would not be a great satisfactory deal, since many serious issues were not addressed (which could be negotiated on this occasion):

> Harnett and Wieker (2013) aptly mentions that, "a company may now secure patent protection in over 40 percent of the world market (by GDP) by obtaining only two patents--a US patent and a Unitary Patent" (Harnett and Wieker, 2013, p.16). The competitors for the patent market are identified are USA and China (European Commission website, 2013). The Unitary Patent hopes to lower the costs from 32 119 euros to 4 725 euros after the transition period, which is 12 years and during that time the costs shall be 6 425 (European Commission website, 2013). Even the reduced costs remain much higher than the presumed competitors, where USA ends at 2 000 euros and China 600 euros (European Commission website, 2013). […]. For the market of future regenerative medicine the competitive advantage shall be determined by the research opportunity, not by patent cost. The IPR protection cost shall be borne by consumers in all cases. The lowering of patent cost does not bind the assignee in an agreement to lower the price of the patented article in itself. A contractual regime should have been created that would promise to lower the price of the treatment and medication systematically, which has not been done. The licensing has been left as the discretion of the assignee as a "contractual license" [Article 8, Regulation (EU) No 1257/2012 of the European Parliament and of the Council of 17 December 2012 implementing enhanced cooperation in the area of the creation of unitary patent protection]. There is no reference made to enable non-commercial downstream biomedical research without infringing the patent. The unitary patent package as a protection tool is a translation of perception of protection of typical technologies. […]. The crisis of patents granted in ethically debated areas shall remain the same. (Jamil 2013a, 38)

The "Press Release" dated 5 May 2015 of the Court of Justice of the European Union while dismissing the actions/claims brought by Spain "against the regulations implementing enhanced cooperation in the area of the creation of unitary patent protection" stated: "unitary patent protection is apt to prevent divergences in terms of patent protection in the participating Member States and, accordingly, provides uniform protection of intellectual property rights in the territory of those States."[138] If Italy and Spain are going to join in this EU patent initiative, will be clear in the coming days. At the time of this writing, they are not part of the new EU patent with unitary effect.

4.5.5 LIMITATION AND PROSPECTS OF THE US PATENTS FOR hSCI

Can a US patent be commercially exploited in all US States and also in Europe? The United States Patent and Trademark Office (USPTO) grants the US patent. Different States have different stem cell research policies. South Dakota has one of the most restrictive policies on stem cell research. Can the US patent be commercially exploited in a State (US State) where they do not allow the research

[138] CVRIA, *Press Release No 49/2015 : Judgments of the Court of Justice in Cases C-146/13, C-147/13 Spain v Parliament and Council, available at* http://curia.europa.eu/jcms/upload/docs/application/pdf/2015-05/cp150049en.pdf (last visited May 29, 2015).

itself? The WARF (Wisconsin Alumni Research Foundation) patents on ES cells can be discussed from the lens of the laws of South Dakota (SD).

The WARF ES cell patents[139] are the early patents on isolation and preparation of embryonic stem cells. Their application is limited to "contributing" in further stem cell researches. The "model species" for the first WARF patent (US Patent No. 5,843,780) on isolation of *primate ES cells* were the "macaques and marmosets".[140] The WARF patent of 2001 (US Patent No. 6,200,806) had its first claim as following: "A purified preparation of pluripotent human embryonic stem cells which (i) will proliferate in an in vitro culture for over one year, (ii) maintains a karyotype in which the chromosomes are euploid and not altered through prolonged culture, (iii) maintains the potential to differentiate to derivatives of endoderm, mesoderm, and ectoderm tissues throughout the culture, and (iv) is inhibited from differentiation when cultured on a fibroblast feeder layer."[141] These inventions (US Patent No. 6,200,806 of 2001) also used "macaques and marmosets" as the model species, but that very patent is the first patent claimed to have discovered the "know-how" of the *isolation and preparation* of human ES cell. The claim no. 9 of the US Patent No. 6,200,806 states its invention as follows:

> "A method of isolating a pluripotent human embryonic stem cell line, comprising the steps of: (a) isolating a human blastocyst; (b) isolating cells from the inner cell mass of the blastocyte of (a); (c) plating the inner cell mass cells on embryonic fibroblasts, wherein inner cell mass-derived cell masses are formed; (d) dissociating the mass into dissociated cells; (e) replating the dissociated cells on embryonic feeder cells; (f) selecting colonies with compact morphologies and cells with high nucleus to cytoplasm ratios and prominent nucleoli; and (g) culturing the cells of the selected colonies to thereby obtain an isolated pluripotent human embryonic stem cell line.[142] (US Patent No. 6,200,806, issued Mar. 13, 2001)

The WARF patent of 2008 (US Patent No. 7,442,548) expressly used the term "human" in the title of the patent which reads as "[c]ulturing human embryonic stem cells in medium containing pipecholic acid and gamma amino butyric acid."[143] Although the other two previous patents, i.e., US Patent No. 6,200,806 (issued Mar. 13, 2001) and US Patent No. 7,029,913 (issued Apr. 18, 2006) used the word "primate" in their title, they both claimed isolation and preparation of human ES cells. Therefore,

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[139] The US Patent No. 5,843,780 (issued on Dec. 01, 1998); US Patent No. 6,200,806 (issued on Mar. 13, 2001); US Patent No. 7,029,913 (issued on Apr. 18, 2006); and the US Patent No. 7,442,548 (issued on Oct. 28, 2008).

[140] United States Patent and Trademark Office, *USPTO Patent Full-Text and Image Database*, *available at* http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=%2Fnetahtml%2FPTO%2Fsrchnum.htm&r=1&f=G&l=50&s1=5,843,780.PN.&OS=PN/5,843,780&RS=PN/5,843,780 (last visited Dec. 10, 2014).

[141] United States Patent and Trademark Office, *USPTO Patent Full-Text and Image Database*, *available at* http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=%2Fnetahtml%2FPTO%2Fsrchnum.htm&r=1&f=G&l=50&s1=6,200,806.PN.&OS=PN/6,200,806&RS=PN/6,200,806 (last visited Dec. 10, 2014).

[142] United States Patent and Trademark Office, *USPTO Patent Full-Text and Image Database*, *available at* http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=%2Fnetahtml%2FPTO%2Fsrchnum.htm&r=1&f=G&l=50&s1=6,200,806.PN.&OS=PN/6,200,806&RS=PN/6,200,806 (last visited Dec. 10, 2014).

[143] United States Patent and Trademark Office, *USPTO Patent Full-Text and Image Database*, *available at* http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=%2Fnetahtml%2FPTO%2Fsrchnum.htm&r=1&f=G&l=50&s1=7,442,548.PN.&OS=PN/7,442,548&RS=PN/7,442,548 (last visited Dec. 10, 2014).

clearly the 3 patents of WARF[144] will serve as primary patents on the subject (isolation and preparation of human ES cell) for further research. Those WARF patents may have problems in exploitation in South Dakota but can be freely commercially exploited in the other States e.g., California, Massachusetts, New Jersey, etc.

Claim No. 9 of the US Patent 6,200,806, issued on March 13, 2001, assigned to WARF covers the following process: "A method of isolating a pluripotent human embryonic stem cell line, comprising the steps of: (a) isolating a human blastocyst; (b) isolating cells from the inner cell mass of the blastocyte [*sic*] of (a)".[145] That embryo (or pre-embryo by some definition) from which the *pluripotent* cells will be derived following the technique of the WARF patent's (US Patent 6,200,806) claim 9, have to be destroyed; because the isolation of the cells from the ICM of the blastocyst will destroy that blastocyst's further development as human organism. This patented isolation and derivation process cannot be used for stem cell research in South Dakota. §34-14-16 of South Dakota Codified Laws states: "Research that destroys human embryo prohibited--Violation as misdemeanor. No person may knowingly conduct nontherapeutic research that destroys a human embryo."[146]

The derivation process of the WARF patent would essentially destroy the embryo from which the stem cells will be isolated and derived, but the further research that will apply the patented technique may not intend or succeed to find a therapeutic application in general. Therefore, any research not having any direct therapeutic application by using the WARF patent will be illegal in South Dakota. However, the SD's (South Dakota Codified Laws § 34-14-19 (2013)), definition of "non-therapeutic research" is the following: "[T]he term, nontherapeutic research, means research that is not intended to help preserve the life and health of the particular embryo subjected to risk. It does not include in vitro fertilization and accompanying embryo transfer to a woman's body or any diagnostic test which may assist in the future care of a child subjected to such tests."[147] So, they allow therapeutic research on the embryo in question for its own benefit. But they prohibit any type of research that destroys or risks this embryo *as a means* to invent downstream therapeutic application for the general population.

Therefore, South Dakota prohibits:

1. Any subsequent/downstream research within South Dakota (SD) that employs the *process patent of WARF* involving production of hESC by means of embryo destruction. No scientist can use the patented WARF methodology of embryo destruction; and

2. No research is permitted using hESC line that was derived by embryo destruction. It does not matter if those cell lines were made within or outside SD. So, the hESC lines made using *WARF process patent* cannot be utilized for conducting research within the State (SD) irrespective of where they were made.

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[144] US Patent No. 6,200,806 (issued on Mar. 13, 2001); US Patent No. 7,029,913 (issued on Apr. 18, 2006); and the US Patent No. 7,442,548 (issued on Oct. 28, 2008).

[145] United States Patent and Trademark Office, *USPTO Patent Full-Text and Image Database*, *available at* http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=%2Fnetahtml%2FPTO%2Fsrchnum.htm&r=1&f=G&l=50&s1=6,200,806.PN.&OS=PN/6,200,806&RS=PN/6,200,806 (last visited Dec. 10, 2014).

[146] S.D. CODIFIED LAWS § 34-14-16 (2013), *available at* http://law.justia.com/codes/south-dakota/2013/title-34/chapter-14/section-34-14-16/ (last visited Dec. 09, 2014). However, the text does not clearly mention, if there were a therapeutic objective *per se*, the research causing destruction of the embryo would be allowed.

[147] S.D. CODIFIED LAWS § 34-14-19 (2013), *available at* http://law.justia.com/codes/south-dakota/2013/title-34/chapter-14/section-34-14-19/ (last visited Dec. 10, 2014).

Since there is nothing like "State Patent," there is no question of granting or rejecting any "South Dakota Patent." Hence, some of the early stage *US patents* on hSCI may not enable the assignee to exploit the invention commercially in *all* US States.

The Enlarged Board of Appeal (EBoA) of the European Patent Office (EPO) decided on November 25, 2008 that the WARF patent on human ES cells isolation and preparation is "unpatentable" as "European Patent" under the Article 53(a)[148] and Rule 28(c)[149] of the European Patent Convention (EPC), 1973.[150] The Enlarged Board of Appeal responded in G 0002/06:[151] "Rule 28(c) EPC (formerly Rule 23d(c) EPC) forbids the patenting of claims directed to products which- as described in the application — at the filing date could be prepared exclusively by a method which necessarily involved the destruction of the human embryos from which the said products are derived, even if the said method is not part of the claims."[152]

Following statement made on behalf of the President of the European Patent Office in G 0002/06, is included in the published "Decision of the Enlarged Board of Appeal" of 25 November 2008:

> The *ratio legis* of Rule 28(c) (formerly 23d(c)) EPC is the prohibition of misuses or the commodification of embryos. […]. The exception to Rule 28(c) (formerly 23d(c)) EPC stipulated in Recital 42 of the Directive should apply in any case where it can be established from the relevant invention that it serves a therapeutic or diagnostic purpose for the used embryo. Usefulness to the individual embryo presupposes that the used embryo is still in existence and is not irreversibly destroyed. […]. In situations where Rule 28(c) (formerly 23d(c)) EPC is applicable, the legislator has predetermined a genuine European *ordre public* and morality, in substance and in time, falling under Article 53(a) EPC, which is binding on the relevant departments of the EPO.[153]

Patent encompassing the destruction of embryo is considered as serving a "commercial purpose" and unpatentable, as it is against the principle of the *ordre public* and/or morality enshrined at the European Patent Convention (EPC) 1973 for the purpose of European Patent at EPO. Although the WARF patents on ES cell derivations did not mention the word "destruction" in their claim language, EBoA rejected the patent on the issue of the *destruction* of the embryo for a *commercial* purpose. The "destruction" was integral to the method of their producing ES cells.

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[148] Article 53(a) states: "European patents shall not be granted in respect of […] inventions the publication or exploitation of which would be contrary to "ordre public" or morality, provided that the exploitation shall not be deemed to be so contrary merely because it is prohibited by law or regulation in some or all of the Contracting States". *Supra* note 26.

[149] Rule 28(c) of the European Patent Convention, 1973 states: "Under Article 53(a), European patents shall not be granted in respect of biotechnological inventions which, in particular, concern the following: [….] uses of human embryos for industrial or commercial purposes". *Supra* note 26.

[150] Case No. G 0002/06. European Patent Office, *Search in the board of appeal decisions database*, *available at* http://www.epo.org/law-practice/case-law-appeals/recent/g060002ep1.html#q (last visited Dec. 11, 2014).

[151] Appellant/Applicant was Wisconsin Alumni Research Foundation (WARF).

[152] European Patent Office, *Search in the board of appeal decisions database*, *available at* http://www.epo.org/law-practice/case-law-appeals/recent/g060002ep1.html#q= (last visited Dec. 11, 2014).

[153] European Patent Office, *Search in the board of appeal decisions database*, *available at* http://www.epo.org/law-practice/case-law-appeals/recent/g060002ep1.html#q= (last visited Dec. 11, 2014).

4.5.6 IMPLICATIONS OF DIVERGENT PATENT FRAMEWORK

There is no international patent. The Patent Cooperation Treaty (PCT) provides a simplified international patent application *procedure* among the contracting States.[154] PCT system does not provide any international patent; there is nothing like that. Patent grant or rejection is the choice of the national office. Therefore, the divergent interpretation of the patentability will continue to exist. However, the divergent patent framework for the hSCI will have certain implications.

- **Mobility of Patients**

The most predictable consequence of different legal landscape of stem cell research and patenting is that the transplants will be available in certain countries and not in all countries. The therapies may not be available in all high income countries too. If it is marketed in any/some of the developing countries, the typical negative impacts heath care tourism creates in the access to health care, shall continue to occur. Affluent foreign patients can exclude the poor locals from accessing the quality health care (Cohen 2011-2012, 3--5). There is also a concern of protecting those health care tourists from malpractices, e.g., administering placebos on them, uncertainty in compensating for medical error (Cohen 2011-2012, 8), etc. Murdoch and Scott (2010, 17) commented that, "[t]ransplants in under- or unregulated jurisdictions have not been tested in animals or in properly phased, blinded, and controlled clinical trials." Patients may end up in such countries to receive an unproven treatment at their own expense to accelerate their health misery. It was reported that from 65 countries, approximately 300,000 women[155] were fitted with industrial grade silicone breast implants (Poly Implant Prothese (PIP)) made by a French company (BBC News Health, 10 Dec. 2013). This implant subsequently caused serious health concerns and many of the women received were Latin Americans.[156] The lesson that can be learned from the PIP incident is that the foreign patients of developing countries receiving cutting-edge but faulty treatment from developed countries may face immense difficulty to access to the proper care to restore their health after they return to their home countries. If the technologies are available only in the country where they received the treatment, their home country might not be prepared for treating them, after they had received inappropriate treatment. It is apparent that the stem cell based therapy will not be available in those countries where the invention will not be IP protected. Uncertainty remains in the EU, if the patients will be covered by their insurance at home country for the treatments that are considered (by the home country) to be the product of unethical medical research, received in other member States. Therefore, with the chance of increasing the mobility of patients, concerns over their heath-safety and quality of care remains an issue.

The fact that the affordability of patients from developed countries seeking treatment in developing country will be high; the locals will find it difficult to access the care in those developing countries.

- **Mobility of Scientists**

There will be a continuous flow of the scientists and researchers towards those countries (or States in case of the US) where the regulatory atmosphere is conducive to stem cell research. Aaron D Levine (2006, 866) reported that, "data suggest the excitement generated by stem cell research and the disparities created by the policy patchwork governing the field may indeed be increasing scientist

[154] At the time of the writing, the number of contracting States was 148 (WIPO: The PCT now has 148 Contracting States 2014).
[155] In some publications, the number appeared higher than this.
[156] Santolo et al. (2014, 462) published "a retrospective MR analysis in 64 patients" of the PIP implants and concluded that, "[t]he results of this double center retrospective study, confirm the higher incidence (36%) of prosthesis rupture observed with the PIP implants, compared to other breast implants."

mobility."

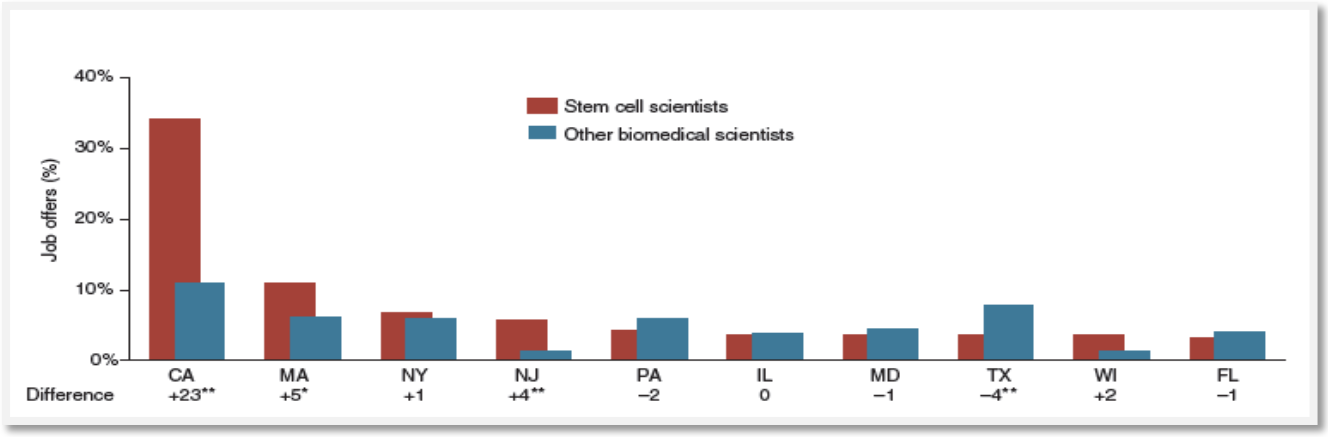

Fig. 4.16 "Stem cell scientists received proportionally more offers for positions in California and other states with permissive research policies." (Figure 1, Levine 2006, 866)

- **Variations in Prices of Medicinal/Drug Products**

The price of the same medicinal/drug product is "different" in different countries. Kanavos et al. (2011, 23--24) published: "Among the EU Member States analysed, Germany, Ireland and Sweden were among those with higher average prices in 2008; Spain, France and Italy had lower prices. The USA is an outlier, as prices of branded medicines have been consistently higher than in Europe, with over twice the price level of the UK in 2008."

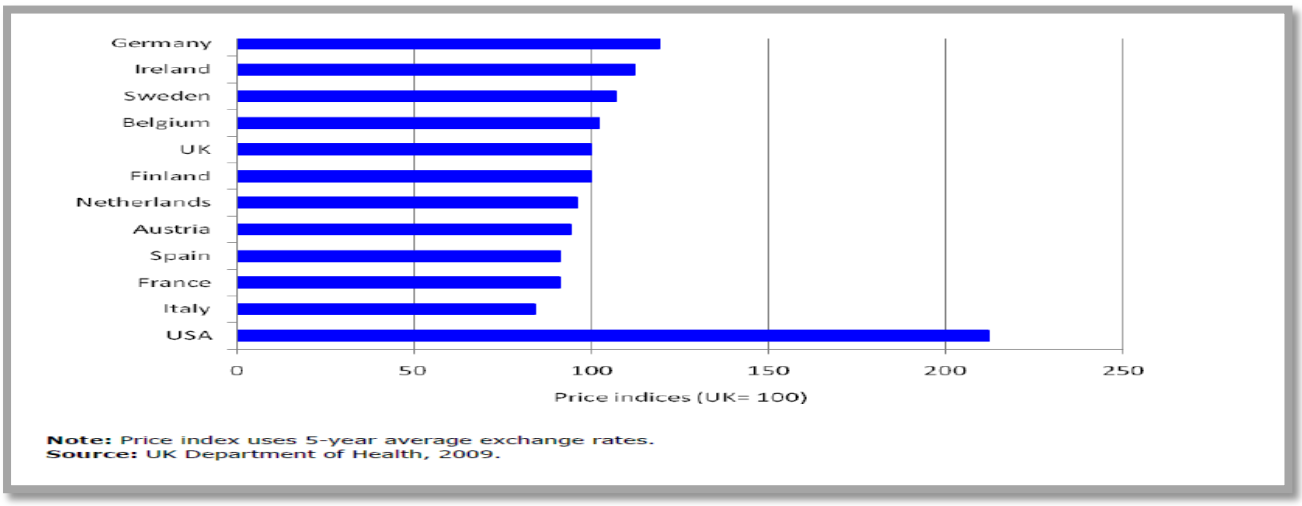

Fig. 4.17 "Price comparisons among EU Member States (and with the USA) for a basket of 150 products; 2008 price index with UK=100" (Figure 6, Kanavos et al. 2011, 23)

There may be number of factors for which the price of the medicine/drug will be higher in one country and lower in another. Patent protection is a contributor of higher drug price but not the dominant player for creating the "variation of price." The demand-supply, size of the market, Government's and insurance's contribution, co-pay with the insurance, Gross National Income (GNI) per capita, local manufacturing ability, parallel trade, Health Technology Assessment (HTA), health care needs and priorities of individual country, etc., may also have relation with the variation of prices. Kanavos et al. (2011, 32) found that, "[t]he main factors leading to price differences include income levels; national (and sometimes regional) regulatory policies for pricing and value assessment of pharmaceuticals; approaches to regulating wholesale and retail distribution; and

taxation of pharmaceuticals, in particular VAT." However, the varying degree of "pre and post grant" costs (fees) of patents may have some links to the "variation of prices," but that claim will require more empirical investigation. As a matter fact, the price differences exist and the "divergence" in the patent framework may not be the dominant reason of "differentiated pricing" or "price variation." Kanavos et al. reported their findings regarding the price differences of pharmaceutical products in the EU States:

> The prices of pharmaceuticals vary across EU Member States: for a basket of 150 medicines, the national averages differ by up to 25%.
>
> For individual pharmaceuticals sold across the EU, price differences are even higher. For patent-protected individual pharmaceuticals, differences as high as 4:1 have been observed between the highest and lowest prices.
>
> Price differences appear even greater for pharmaceuticals whose patents have expired, as generic versions increase market competition. For these medicines, differences as high as 16:1 have been observed among Member States for individual generic pharmaceuticals. (Kanavos et al. 2011, 18)

Kanavos et al. encountered that "manufacturers of generics may decide not to enter smaller markets" (2011, 14).[157] In order to offer the citizens cheaper medicine and materialize the benefits of generics, the "local manufacturing ability" of a country is vital. In case of stem cell based therapies, "manufacturing technology transfer" may be an important issue.

[157] Some small European markets like Lithuania are in great need of cheaper medication, as the purchase capability, average income of the working class and pensions of the elderly citizens are very low. Despite patented drugs are more expensive in Germany compared to other EU countries (Kanavos et al. (2011, 24), the purchase capability of the population is also high.

CHAPTER 5
QUALITATIVE DATA ANALYSIS

5.1 QUALITATIVE DATA ANALYSIS

Only some of the respondents made "comments/other opinions" which could be analyzed qualitatively.[1] The conventional content analysis of the perceptions and views of the expert respondents also contributed to the formulation of the set of recommendations.

Interpretation of the Major Key Themes derived from responses to question no. 1:[2]

The respondents have emphasized the ethical controversies surrounding the hESC research. Some of them have viewed embryo as equal to human and "destruction" of embryo as "killing" of life. Both the "use" and "destruction" of human embryo for hSCR are opposed by some of the respondents. But some of the respondents see the hSCR as any other type of scientific research and finds that promising application exist. Other alternative techniques involving somatic/adult stem cell research is acceptable to some of the respondents.

Many respondents are against embryonic stem cell research because they have empathy for the embryo. They are more into the rightness and wrongness of the action. Use of embryo as "offensive endeavor" for hSCR is reiterated in the responses of this question.

Interpretation of the Major Key themes derived from responses to question no. 2:[3]

Many divergent opinions surfaced. There were both recognition of the embryo as a "cellular entity" and conferring the embryo with some kind of "rights" that are different from that of human being. There is also tendency of complete denial of rights to the embryo. At the same time there is tendency of not drawing distinction between the embryo and human.

It was asserted that there is no consensus at which moment the developing entity shall be termed as an "embryo"; a conclusive definition of embryo is believed not to exist. In the absence of "soul" as the vital component, the embryo is also not considered as a human.

Embryo, human body and human life are also deemed as integral parts of each other and collectively they form a human being. The tendency of ascribing the embryo with "gender" signifies the endowment of a legal status to the embryo.

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[1] The questionnaire mentioned: "The responses of the participants/respondents in this study shall be analyzed for the purpose of the Doctoral Study conducted by ARIF JAMIL[…]. The information provided can be used/published by the Research Fellow and CIRSFID, University of Bologna; otherwise shall be considered confidential and the identity of the participants shall be kept anonymous, unless required to prove the authenticity of the study. The participants/respondents hereby consent to take part in the study." Appendix II: Questionnaire.

[2] Some of the words/phrases used/mentioned within quotation in the major key themes and their interpretations are the exact words/phrases used by the respondents. Appendix V: Qualitative Analysis (Qualitative Content Analysis (QCA)).

The questionnaire mentioned that, "the identity of the participants shall be kept anonymous, unless required to prove the authenticity of the study." Appendix II: Questionnaire.

[3] *Supra* note 2.

Non-existence of a universality of perceptions was also asserted. A different and special status of the embryo from the human was also acknowledged. The health, safety and well-being of human being were given priority, when it comes to usage of embryo in scientific research.

Interpretation of the *Major Key Themes* derived from responses to question no. 3:[4]

Respondents thought that it is acceptable to employ embryo in limited circumstances, but the application is unethical in general and did not support using embryo as massive therapeutic tools.

The embryo/fetus is believed to be incapacitated but still possesses some rights. Balance is thought to be required between the conflicting interests of the entities, i.e., the "embryo" (which has the right to be protected) and the "society and individual" (who will gain therapeutic benefits from the research).

Respondent supported the use of embryos in research that are redundant for clinical purposes (e.g. IVF) and considered the creation of *in-vitro* embryo exclusively for research purposes as unethical. In this case the rationale or reasonableness of the action was viewed from the perspective of proportion and reality.

Respondent highlighted the scientific absence of the precise moment when the fertilized entity shall be termed as embryo and emphasized on the "stages of development".

Respondent also identified embryo at early stage as a "biological material of human origin" and as a different component from the human being or human body and thought that "there is nothing unethical about its use" and was inclined to use a positive connotation for the usage/practice and hence, preferred to use the term "use" instead of "destruction."

It was emphasized that fulfilling certain conditions like good scientific reason, informed consent from embryo donors and careful monitoring are critical.

The respondent asserted that alternative sources are available. Cord blood is suggested as a substitute source of embryonic stem cells.

Interpretation of the Major Key Themes derived from responses to question no. 4:[5]

As this question was exploring the personal experience of the respondent, their professional experiences came to the fore. Respondent being medical professional admitted the inadequacy of the medical treatment. Effectiveness of a particular medical treatment can be subjective due to variability in the biological systems in individuals, as believed by the physician respondent. Respondent also asserted that medical professionals always encounter the non-efficiency of medical treatment.

As metaphysician, the respondent believes that alternative approaches of treatment may exist. Limitation exists in the conventional approach of treatment taken in the biological science. Metaphysical science may offer some solutions where biological science is ineffective.

[4] *Supra* note 2.
[5] *Supra* note 2.

Interpretation of the Major Key Themes derived from responses to question no. 5:[6]

The question tested two things:

- If the respondent despite being for/against the stem cell research would accept the therapy for their dear ones (how objective they are); and

- How they would like to access it (means of accessibility).

Many of the respondents expressed that they will accept it (either they were negative or positive about stem cell research) and they will access it through the conventional means, e.g., free care from the State, insurance coverage "entirely or partially", personal expenses. But the "State" as service provider was also observed as popular choice. Respondents expected that the costs should be reasonable, if they are to access through personal resources.

Some of them were more concerned about the safety and efficacy of the treatment in scientific terms. They will not accept until the therapy is proven to be effective.

Response to this question may have been influenced by the health care system of the respondents' country of origin and reflective of their personal experience. Higher number (70.97%) of the respondents come from the country of high economy group.

Interpretation of the Major Key Themes derived from responses to question no. 6:[7]

This question intended to see why they would support or reject patent for hSCI. The respondents provided many insights related to patenting aspects of hSCI.

The respondent was found to be in favor of stronger IP rights and suggested "*ad hoc* data exclusivity rights" if hSCI are protected as biotech inventions. Also reminded that exceeding the 20 years' term of protection would affect access to therapy for the patients in less developed countries. Respondent suggested simpler IPR protection framework than patent due to ethical constraint in the hESC research, increasing litigation and opposition.

The respondent expressed skepticism about the appropriateness of the patent system for life sciences but he did not reject the patent system. The respondent also sees it (patent) slightly misfit for protecting the living organism and raises concern regarding the possible adverse social effects. With changes of time, "how patent is adaptable to newer inventions in life science" was raised as question. Respondent did not accept evergreening of patent, i.e., taking new patent for already known technology (for example, second medical application of known drugs).

Respondent found to have supported IP protection in the form of "moral rights" only aka., right of recognition and integrity but rejected the commercial feature of the IPR for life science inventions/innovations.

Respondent observed that patent has two implications:

1. It is an incentive for research and development; and

[6] *Supra* note 2.
[7] *Supra* note 2.

2. It is a barrier for further research in connected fields of knowledge (limits the parallel and downstream research freedom).

The respondent did not support the patent protection of inventions derived from living entities; because we are supposed to understand and gather knowledge from it.

Respondent believed that most researchers are driven purely by curiosity and altruism; doctors and lawyers need to understand the noble purpose behind the innovation.

Interpretation of the Major Key Themes derived from responses to question no. 7:[8]

The respondent does not believe that a new creation can be made within the realm of life science. And it was also considered that IPR should be used to protect only new creations, human stem cell based inventions/innovations, therefore, cannot be patented because they are not new creations.

Respondent had the opinion that stakeholders of health care should be more pro-people, focusing more on how to provide affordable care and therapy to people rather than emphasizing on gaining financial incentives derived from patented technology. Respondent favored reduced commercialization in health care sector, in general.

Respondent did not support any protection framework that will have a commercial feature and inclined to rely on government's money as the source of funding for research. Respondent believed that research targeted to health care is done for humanity and is willing to recognize the inventor but will not support the commercial features of the IPR or patent.

Most of the respondents making comments in response to this question had one common concern i.e., commercialization through IP. They emphasized that inventions having health care implications should be pro-people and non-commercialized. Hence the feature of any new protection framework should not be typical patent or traditional expressions of IP.

Interpretation of the Major Key Themes derived from responses to question no. 8:[9]

This question tested the respondents' opinion about tenure/length of IP protection for the hSCI. Respondents making other opinion supported 20 or more years of IP protection for the hSCI and cited as justifications:

- equivalent of current patent's tenure; and
- the formality of regulatory approvals.[10]

[8] *Supra* note 2.
[9] *Supra* note 2.
[10] The response (comment of the respondent) indicated that the time spent in regulatory approval, if deducted from the term of protection, the IPR owner does not get enough time to exploit the invention commercially in the market.

It is worth mentioning here that the drug developer enjoys patent right and regulatory data exclusivity right simultaneously. The IPR on the core content of the invention remains in force until the expiry of the last one (whichever ends later).

Interpretation of the Major Key Themes derived from responses to question no. 9:[11]

Respondent will allow a very limited use of human embryo for research and innovation in cases of serious disorder; not for large scale commercial and industrial application (will allow limited therapeutic application).

Respondent also supported (suggested) development of therapeutics by using human embryo, when they are conducted by Academic/NPO/Government.

Respondent suggested employing only redundant embryos that are anyway destined for destruction, which indicates that she does not support *in-vitro* development of embryo and its deliberate destruction for the purpose of research and therapy.

Respondent was inclined to allow the application of human embryo for research targeted to find cure or drug development but not through commercial channels.

Respondent suggested conducting stem cell research by using the cord blood, instead of human embryo. The respondent believed that human embryo and cord blood are equivalent sources of any type of stem cells and hence there is no need to use embryo, in addition people who might object to application of embryo might not do so if the research involves cord blood instead of human embryo. He presumes that cord blood would invoke less or no ethical concern as opposed to using human embryo.

It appears that non-commercial channel conducting the research, developing and distributing the therapy is the most favorite choice. They also suggested using alternative source of stem cells or redundant embryos for research (destined to destroy). Their comments seemed to be opposing the large scale commercial use of human embryo. They also suggested a limited use for therapeutic purposes.

Interpretation of the Major Key Themes derived from responses to question no. 10:[12]

Respondent asserted that the contractual arrangement is the determining factor for "who will own the IPR".[13]

The respondent thought that the donor of cell line, if not included as the owner of IPR of the inventions from his/her biological sample, should receive a compensation. The respondent is suggesting to offer a *"just" compensation* for commercially developing an invention from the samples of a research subject.

Respondents supported the "moral right", not an economic right (as the moral right is only limited to the recognition, not extended to the commercial exploitation). The respondent considered the philanthropic aspects, rather than the conventional reality of the drug development and behavior of the market. Scientist/Inventor, funding organization and patients were suggested to be entitled to the right of recognition (moral right) only.

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[11] *Supra* note 2.
[12] *Supra* note 2.
[13] In employer and employee setting, the ownership of the patent is taken by the employer organization/university (as "assignee") and the scientist is awarded the recognition for the invention (as "inventor"). It is a common practice and it depends on the contract between the employer and the employee. In some cases, the inventor is also seen as the assignee with the employer.

The entitlement of IP was seen as depending on the funding sources (if public funding is the source of research, then the entitlement should be awarded to scientist/inventor and public and eventually the invention should be in the public domain).

Respondent is willing to award the IPR to the inventor/scientist only and thought that the employer organization/university makes no intellectual contribution to the hSCI and most of their expenses are covered by "grant". Merely for the facilities they provide to the researchers, they should not be awarded with the IPR of the hSCI.[14]

Interpretation of the Major Key Themes derived from responses to question no. 11:[15]

At present, multiple techniques of derivation of ES cells are available to the world. Two prominent techniques use the embryo directly. One, derives ES cell by embryo destruction and another, derives from the blastomere cell of the pre-implantation stage embryo. The question explores the *benefits vs. risks* of employing the embryos.

The respondent believed that the benefits of human embryonic stem cell research outweigh the risks and cost associated with it, as this type of research has practical application in curing many diseases which currently has no cure. Again they also seem promising for rare diseases where a group of afflicted patients can afford to pay for the research and therapy.

The respondent does not notice any inherent risk of stem cell research employing human embryo. However, when it comes to cost, respondent emphasized on conducting economic and viability studies making sure that Government money (i.e., public resources) spent is well justified and brings out fruitful outcome.

The respondent believed that the non-specialized and *pluripotent* nature of hESC make them an excellent candidate for potential therapeutic interventions on wide conditions. The benefits outweigh the risk and costs in hESC research as well as contemporary medical research applying other techniques and thus reducing time and costs of other life science researchers.

The respondent considers that the benefits would be more than the risks and cost associated to it only if this type of research undergoes strict and harmonized regulation as to how these studies are conducted employing hESC.

The respondent considers that this type of research is beneficial mostly because of effective therapeutic interventions obtained down the road which help to prolong the life of those "who are already living." She indicates that the advantage may contribute to the increase of life expectancy.

[14] A big proportion of this fund secured by an inventor is mandated to flow into the research institutions he/she is affiliated to, which is usually termed as Indirect Cost (IDC) (also known as Facilities or administrative rates). The university spends this amount to provide the administrative and infrastructural support to the inventors and academics. For example, the current IDC rate of federally secured grant is 50% for conducting on-campus research at the University of Florida (UNIVERSITY of FLORIDA, Office of Research: F&A Rates (IDC) 2015). What it means is that 50% of the grant money brought in by an academic through fierce competition goes to the University by default, he/she has to plan the research based on the rest 50% of fund. This mandate is a serious pressure for an inventor trying to secure enough funds to carry out research in a timely manner and making due progress. But when a patent is granted, it is often assigned to the university. The respondent did not support this current practice of ownership for the above mentioned reason (most likely), mostly prevalent in the US.

[15] *Supra* note 2.

The respondent believed that there are inherent risks and variable amount of costs associated with every kind of medical research and hESC research is no exception. If risking the embryo serves to invent a useful therapy that can benefit human life, health and the overall society, the respondent thinks it is important to do so.

The respondent believed that the benefits of hESC are contingent upon costs associated with research and affordability of the final therapy as well as the time required to bring the research outcome from laboratory to the clinic.

Although the respondent considered the hESC research as important but had reservation to generalize the risks, benefits and possible consequences of every hESC research but instead believed that each scientific case would vary considerably on these parameters and deserves special scrutiny to determine the individual risk and benefit. The respondent reminded that the answer of this question depends on the "context" and "circumstances" of each case; there is no universal approach to this issue.

The respondent believed that the results of basic science should be promising enough to warrant further applied research and considered that hESC as an applied research is employing human embryo without having solid and convincing basic science research data.

The respondent also did not support stem cell research that involves destroying or putting the human embryo at risk. Respondent seems to acknowledge the dignity and rights of human embryo in parallel to a fully developed human being.

The respondent considers stem cells derived from cord blood are equivalent in function and potency to that of hESC and there is absolutely no need to employ human embryo in this type of research.

The respondents highlighted context, circumstances, case-by-case evaluation, regulatory control, sound data, therapeutic potential, economic and viability studies, alternative stem cell researches etc., in assessing the "benefit v. risks" of employing embryos in stem cell research.

Interpretation of the Major Key Themes derived from responses to question no. 12:[16]

The question intended to examine if imposing *legal obligation* on the IP rights of the IPR owner can bring a just and right balance between "ensuring availability of medication/treatment at a reduced cost" and "incentive for the IPR right owner of hSCI". The examples of legal obligation cited were "'licenses on easy terms', 'compulsory licenses' and 'technology transfer'". The involvement of "public health care sector," issuing licenses in favor of local pharmaceutical companies/hospitals, manufacturing and production of therapies and medications locally, were among the suggested options. Very few other opinions were encountered. Respondent stressed importance on the context of the country. In some countries waste of resources in corruption and unnecessary programs may be the reasons of high drug price and the high price of drugs may have been used just as an excuse to blame the patent for contributing to high costs. The respondent considered that *transparency and proper utilization of public resources* are keys to realizing these goals in countries like Mexico, instead of issuing any forms of legal obligation but also additionally reminded that these measures may be beneficial for other countries with different context.

[16] *Supra* note 2.

The respondent did not support mandating or imposing legal obligations on patent holder, rather believed that public authorities should be judicious on enforcing it where appropriate based on sophisticated and flexible conditions.

The respondent indicated that there is need to make improvement in the IPR mechanism in order to facilitate access to the medication. It appears that he finds that there are some impediments caused by IPR in accessing the medical innovations and there are "flawed" systems in place, when it comes to inter-relations between the IPR and access to medications. Respondent considered that "access to therapies" / "products borne out of medical innovations" should not remain restricted but rather be made available to everyone. Respondent also asserted that hSCI / "life science inventions" are not new creations and should not be IPR protected in the first place.

Interpretation of the Major Key Themes derived from responses to question no. 13:[17]

In order to implement this idea, the public need to be well informed. It means that the public must have access to the information regarding the proportion of the different expenses incurred for the product development, e.g., R&D, IP/Patent related fees and costs, marketing costs, incentives for investing in future research, etc.

Most of the other opinion were negative about seeking public opinion and the common reason stated is *the lack of information to the public* to enable them to make any solid difference through sensible opinion.

Respondent indicated that, if there is any issue related to "*ordre public* and/or morality" (obvious public outcry) then public opinion can be sought, otherwise it's not important.

The respondent did not support the idea of seeking public opinions to measure the post marketing impacts but suggested that information should be made available to the consumers *a priori* so that they can learn more about the therapy and make informed decision whether or not to purchase and use it.

The respondent thought that the civil society should have the legal instruments available so that they can resort to adjudication against undue commercial exploitation. Respondent does not seem to find independent public opinion very effective as a means to giving post marketing feedback or any positive or negative responses.

Respondent assumed that embryo's source is central to public interest and not access, affordability, safety or efficacy of the therapy (in case the therapy is developed from hESC), hence had the opinion that the common people of a particular country might not object towards an imported therapy if the embryo used isn't derived from their countrymen.

Respondent also suggested seeking "public opinion" / "public consultation" prior to commercial exploitation. It remains unclear what purpose it will serve though, in terms of the key aspects of therapy i.e., access, affordability, long term safety and efficacy. Drug pricing rationale and policy is never fully disclosed to the consumer. Hence, what purpose might pre-marketing public response serve, if they (public) don't have any knowledge and decision making role in drug pricing, is not clear from that opinion.

The contents of the overall summary of the Qualitative Content Analysis (QCA) can be found in ch. 6.

[17] *Supra* note 2.

CHAPTER 6 : SUMMARY

6.1 SUMMARY OF ETHICAL AND LEGAL ANALYSIS

The monograph is comprised of both theoretical (comparative legal and ethical analysis of the purview of the stem cell research and patenting in select juristictions) and empirical (qualitative analysis) parts. The *interpretation of the Major Key Themes* derived from responses to questions related to ethical and legal issues (question nos. 1, 2, 3, 4, 5, 11) can be found in ch. 5. The Major Key Themes derived from responses to questions related to ethical and legal issues appear in ch. 3, as and when it deems appropriate to provide more insights into the discussion. The o*verall summary of the Qualitative Content Analysis (QCA)* of the questions related to ethical and legal issues appears in ch. 6 together with the summary drawn from the theoritical discussion (that took place in chaps. 2 and 3).

Following are the summary analyses of both theoretical and empirical (qualitative) analysis on the ethical and legal issues in hSCR:

I. The *most advanced stem cell research techniques were investigated*.[1] The comprehensive investigation revealed various legal and ethical issues involved in these techniques.

Overall summary of the Qualitative Content Analysis (QCA) reveal the respondents' Opinions prevailing on impression/prejudice about hSCR:[2]

- Differing opinions prevailing on impression/prejudice about hSCR.
- Some are prejudiced, empathetic to embryo, destruction was referred to as "killing," thought hSCR politically and ethically controversial, will approve somatic/adult stem cell research.
- Some considered hSCR as any other kind of research, and as a promising area for therapy.

Overall summary of the Qualitative Content Analysis (QCA) reveal the respondents' Opinions prevailing on benefits vs. costs and associated risks of hESC research:[3]

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[1] See ch. 3.1 HUMAN STEM CELL RESEARCH: VARIOUS TYPES AND THEIR ETHICAL AND LEGAL ISSUES.

[2] Some of the words/phrases used/mentioned within quotation in the major key themes and their interpretations are the exact words/phrases used by the respondents. Appendix V: Qualitative Analysis (Qualitative Content Analysis (QCA)).

The questionnaire mentioned that, "the identity of the participants shall be kept anonymous, unless required to prove the authenticity of the study." Appendix II: Questionnaire.

[3] *Supra* note 2.

- Two contrasting ideas regarding relative benefits vs. costs and associated risks of hESC research: some were not supportive of employing human embryo at all, whereas others found it beneficial in curing disease and increasing life expectancy.

- A proper balance of conflicting interests of embryo and human beings rests upon: *specific study context, sound basic science data to substantiate applied/clinical research*, the costs of research relative to benefits it might bring to the society and ensuring strict regulatory oversight.

II. Adult stem cells have very limited potential in application and have no significant ethical controversies.[4]

III. The *NT-ESC and hpSC will require healthy egg procurement*[5] and may create perfect environment for human egg trading.[6] NT-ESC/SCNT and hpSC will require healthy human eggs for the derivation of the stem cells. Apart from the ethical concern, the health risks of the donor women also deserve attention. The short and long-term effects of the procedure and artificial ovulation may cause harmful consequences to the donor's health. Egg donation is not a very simple process; it involves harsh reality. It is called "donation" but without compensating enough, there will be dearth of donors. Eventually women in financial need will be exploited for the process. Loane Skene (2010, 239) wrote: "Many human eggs will be needed and women who may wish to be donors will no doubt be deterred when they are told about the risks of donation."

IV. The embryo cloning procedure described by Tachibana et al. (2013) with a modified SCNT protocol involves creation of *a patient specific "cloned embryo"* through the "fusion" of the *"patient specific somatic cell"* (serving as the nuclear donor of the resulting "cloned embryo") and *"enucleated egg"* (donated by healthy donors).[7] This protocol does not employ an existing/already available embryo from IVF facility; rather uses the "cloned embryo" propagated to the blastocyst stage in order to derive the patient

[4] See ch. 3.1.1 ADULT STEM CELLS AND SOMATIC CELLS.

[5] Tachibana et al. (2013, 1236) published on NT-ESC (SCNT) derivation process: "Anonymous egg donors of ages 23–33 were recruited [...]. Responding women were screened with respect to their reproductive, medical, and psychosocial health. […]. Egg donors were financially compensated for the time, effort, discomfort, and inconvenience associated with the donation process."

[6] See chaps. 3.1.2.2 REPROGRAMMING BY SOMATIC CELL NUCLEAR TRANSFER AND THE DIRECT INTRODUCTION OF TRANSCRIPTION FACTORS; 3.1.2.3 STEM CELLS DERIVED FROM THE PRE-IMPLANTATION STAGE EMBRYO'S BLASTOMERE CELL, HUMAN PARTHENOGENETIC STEM CELLS, ETC.

[7] The purpose of this modified SCNT protocol is *therapeutic cloning* (to derive patient specific NT-ESC) and *not reproductive cloning*. The blastocyst, instead of implantation into uterine wall, was cultured in vitro to isolate NT-ESC. This isolation, therefore, essentially destroys the integrity of the blastocyst (the *zona pellucida* is destroyed in vitro by protease treatment and ICM is disintegrated during culture) (Tachibana et al. 2013, 1236--37).

specific NT-ESC. The NT-ESC (SCNT) derivation process destroys a "cloned embryo" the potential of which is presumed, not decisively established yet.[8]

V. *ESC derived from the blastomere of pre-implantation stage embryo raises different ethical concerns.*[9] If the biopsied embryo is implanted, it may compromise the health of the embryo and resulting child/human and the consequences of such procedure on the biopsied embryo is largely unknown. If the biopsied embryo is implanted, it can/may be viewed as a "commercial and unnecessary" intervention/action (to the embryo itself) in the process of normal development of an embryo. However, they may derive *totipotent* cells (in some instances), which are (likely) capable of developing into a complete organism. The presumed therapeutic benefit for the embryo itself (or resulting child/human) of preservation of autologous ES cells might be *devoid of enough apprehension* for the justification of action.

The "EXAMPLE 5" of the United States Patent No. 8,742,200, issued on June 3, 2014 described "Derivation of Embryonic Stem Cells without Destruction of the Embryo" as following: "The zona pellucida is disrupted using either Acidic Tyroides solution or multiple Piezo-pulses and an individual blastomere is mechanically separated from each denuded embryo [...]. The embryos are subsequently cryopreserved."[10] The example states that after the derivation they were cryopreserved.

How cryopreservation (be it permanent or temporary) of the remaining embryo relieves from the ethical objection around the embryo destruction? *Are we convinced that the dignity of the embryo is protected, if it is cryopreserved and/or "used" in research, instead of "destroyed" for research*? The "cryopreservation of embryo" (after "biopsy" / "blastomere cell extraction") *is not a better substitute of "destruction of embryo,"* for the understanding of moral philosophy.

The extraction of *totipotent* blastomere cell from the pre-implantation stage embryo calls for ethical evaluation in embryo related research. There remains concern over the health of the biopsied embryo and resulting child/human, if implanted. If it is conducted concurrent to PGD, the objective for doing PGD[11] and the objective of derivation of ESC from the extracted blastomere cell, are very different. How ethical this use of the embryo is, i.e., propagation of stem cells from the cells of the "to be implanted embryo" (if implanted later; even if done concurrent to PGD), if it is not truly useful to the embryo itself? The "EXAMPLE 6" of United States Patent No. 8,742,200, issued on June 3, 2014 mentioned: "The separated blastomere undergoes cell division. One progeny cell is used

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[8] See ch. 3.1.2.2 REPROGRAMMING BY SOMATIC CELL NUCLEAR TRANSFER AND THE DIRECT INTRODUCTION OF TRANSCRIPTION FACTORS.

[9] See ch. 3.1.2.3 STEM CELLS DERIVED FROM THE PRE-IMPLANTATION STAGE EMBRYO'S BLASTOMERE CELL, HUMAN PARTHENOGENETIC STEM CELLS, ETC.

[10] United States Patent and Trademark Office, *USPTO Patent Full-Text and Image Database, available at* http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=%2Fnetahtml%2FPTO%2Fsrchnum.htm&r=1&f=G&l=50&s1=8,742,200.PN.&OS=PN/8,742,200&RS=PN/8,742,200 (last visited June 19, 2015).

[11] PGD is conducted to investigate the genetic abnormality potentially harmful for the optimum development of the embryo. However, questions remain on "if" and "how" "safe and effective" PGD is, to ensure a healthy baby with normal genetic makeup.

for genetic testing and a different progeny cell is cultured as in Example 1 to produce a human ES cell."[12]

Chung et al. (2008, 133--16) stated that they used *early stage* ("cleavage-stage" (Chung et al. 2008, 115)) embryo and took out blastomere by embryo biopsy. The blastomeres taken out can be cultured to produce ES cells using their methodology and these cells can be used further for research and therapy. Chung et al. (2008, 116) mentioned: "Here we clearly show that hESC lines can be derived without embryo destruction and that the biopsy procedure did not appear to interfere with subsequent good blastocyst development of the parent embryo." Chung et al. (2008, 115) also cultured the remaining biopsied embryo and allowed it grow to the blastocyst stage. These blastocysts were shown to be normal in characteristics and later cryopreserved. *Unless a/the cryopreserved blastocyst grown from a biopsied embryo is shown to be successfully implanted and produce live birth (without problems (any developmental defect/abnormality) caused to the biopsied embryo/fetus/resulting child or human), it is not very different from "embryo destruction"* or simply "allowing the usage of an embryo" as a "means" to propagate ES cells. It may be a *methodological improvement but still cannot bypass the ethical barrier*. The embryo was grown to the blastocyst stage and then cryopreserved, instead of destruction or implantation.[13] They showed that they could grow the biopsied embryo to the blastocyst stage; the reason (justification) they claim it to be "normal." Therefore, for the same reason the biopsied embryo should be able to result to live birth without developmental abnormality in order to claim that the biopsy does not have adverse impact and the embryo remained normal. But they did not proceed towards "implantation", instead "cryopreserved" the biopsied embryo.

PGD by embryo biopsy is carried out in conjunction with IVF for reproductive purpose, in limited circumstances. If the purpose is strictly research, not benefitting the embryo being biopsied, should it still be considered ethical? Unless they are expecting any long-term need of ES cells (for the embryo biopsied) in advance, what is the purpose of deriving ES cells from the embryo?

VI. There is a *very thin line of difference between therapeutic cloning* (by SCNT) and the reproductive cloning.[14] If the embryo/pre-embryo (developing *in-vitro*) instead of deriving ES cells (by destroying from the blastocyst stage) is implanted and brought to term, it will be "human cloning." Large prohibition exists against human reproductive cloning.

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[12] United States Patent and Trademark Office, *USPTO Patent Full-Text and Image Database, available at* http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=%2Fnetahtml%2FPTO%2Fsrchnum.htm&r=1&f=G&l=50&s1=8,742,200.PN.&OS=PN/8,742,200&RS=PN/8,742,200 (last visited June 23, 2015).

[13] Chung et al. (2008, 115) mentioned: "The remaining biopsied embryos were allowed to continue development and were frozen at the blastocyst stage."

[14] See ch. 3.1.2.2 REPROGRAMMING BY SOMATIC CELL NUCLEAR TRANSFER AND THE DIRECT INTRODUCTION OF TRANSCRIPTION FACTORS.

VII. *Stem cell research policies are very divergent*.[15] Although the Federal Policy on stem cell research is relatively liberal, policies in different States of the USA are different from each other. California, Massachusetts and New Jersey follows liberal policies, whereas Texas and South Dakota are very restrictive. In Europe, in comparison to the USA, more restrictive policies are prevalent. However, at State level in Europe, significant differences can be observed. Italy and Lithuania have very restrictive stem cell research policies, whereas German policy is restrictive yet allows the research subject to certain conditions. Spain and UK have relatively liberal policies on hSCR in Europe.

VIII. Following techniques may be said to encompass the human embryo's use:[16]

- Derivation of ESC from the ICM of the blastocyst (by *destruction of the embryo*);
- Derivation of ESC from the extracted blastomere cell (also *totipotent*) of the *pre-implantation stage embryo*;
- Derivation of patient specific nuclear transfer ES cells (NT-ESCs) (by embryo cloning and subsequent destruction of the "cloned embryo").

None of them are ethically objectionable for the purpose of patenting in the USA. In Europe, the first one is rejected for EP and the fate of second one is not yet known. Are both the uses ethically objectionable? Which one is more objectionable? Which one may have further negative implications? Answer to these questions depend on ethical and scientific perceptions. Some countries accept those experiments as scientific endeavor and some find it morally disturbing. Many countries accept the stem cell research with IVF redundant/donated embryos.[17]

Overall summary of the Qualitative Content Analysis (QCA) shows how the respondents commented on the definition and rights of "embryo":[18]

- No conclusive definition of "Embryo" exists. Some regarded it as a cellular entity with no soul. Embryo, human body and human life were claimed as integral parts of each other.

- Differing perceptions on embryo's right: from complete denial of any rights to conferring some rights to embryo.

- A special status and rights was also acknowledged for embryo but the health, safety and well being of human beings given priority over that of embryo.

[15] See ch. 3.2 HUMAN STEM CELL RESEARCH: LEGAL LANDSCAPE.
[16] See ch. 3.1.2 HUMAN PLURIPOTENT STEM CELLS.
[17] Some of them (e.g., abandoned and redundant) are destined to be destroyed.
[18] *Supra* note 2.

Overall summary of the Qualitative Content Analysis (QCA) also shows how the respondents commented on the use (application) of human embryo:[19]

- Supported research using embryo targeted to developing therapy to serious/rare disorders.
- Opposed large scale commercial use of human embryo.
- IVF redundant embryos can be used. Opposed in-vitro embryo creation with an intention to destroy and use the embryo in research. Alternative source of ES cells suggested (e.g. cord blood).
- Therapy development pursued by academic/NPO/Government bodies preferred.

IX. *Which pluripotent hSCR (hESC, NT-ESC/SCNT, hpSC, iPSC) is free from the ethical debate?*[20] *How do we improve the situation?* All of the techniques have different degree of concerns either at the *research process* or during the *clinical trial and application*. Some of them have *substantially* lower degree (or no) of ethical constraints in the research process, e.g., iPSC. The other alternative hPSCR techniques will have concern around egg donation and health of the implanted embryo. Protection of women's health is a concern for the NT-ESC and hpSC research. The wellbeing of the embryo biopsied is a real concern (if implanted after biopsy) for the technique that derives ES cells from the single blastomere of the pre-implantation stage embryo. *Therefore, strict or liberal, whatever philosophical approach is taken at the policy level, there has to be a strict monitoring to ensure the full compliance with the policies adopted and those policies need to be reflective of people's choices.*

X. Many arguments exist that support that human embryo should be protected.[21] It is also a fact that many degenerative conditions and diseases do not have cure at present. Therefore, in ideal situation, the therapeutic application oriented all human SC research should continue subject to the evaluation of the ethical issues involved.[22]

Overall summary of the Qualitative Content Analysis (QCA) reveal the respondents' Opinions prevailing on inadequacy of conventional medications and alternative approaches:[23]

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[19] *Supra* note 2.
[20] See ch. 3.1.2 HUMAN PLURIPOTENT STEM CELLS.
[21] See chaps. 3.1.2.1 EMBRYONIC STEM CELLS; 3.1.2.2 REPROGRAMMING BY SOMATIC CELL NUCLEAR TRANSFER AND THE DIRECT INTRODUCTION OF TRANSCRIPTION FACTORS; 3.1.2.6 HUMAN EMBRYO FOR THE STEM CELL RESEARCH: ETHICAL AND LEGAL DILEMMA; 3.2 HUMAN STEM CELL RESEARCH: LEGAL LANDSCAPE.
[22] See ch. 3.1 HUMAN STEM CELL RESEARCH: VARIOUS TYPES AND THEIR ETHICAL AND LEGAL ISSUES.
[23] *Supra* note 2.

- Inadequacy of conventional medications often encountered by medical professionals.

- Efficacy of treatment highly subjective. Biological systems in person to person vary considerably.

- Conventional approaches based on biological science have limitations.

- Alternative approaches (e.g. metaphysical science) may offer some solutions.

Therefore, human sufferings and sacrifice of embryos can be minimized by resorting to the best alternatives. An embryo should not be subjected to *unknown risks*, if it is not destroyed after derivation of the cell from it. The Oviedo Convention does not permit *creation of embryo* for research but the *in vitro* research on embryo is allowed,[24] provided that the adequate protection of the embryo is ensured by the particular country. Therefore, the destruction and some particular manner of use of the embryo can conflict with the idea of "protection of the embryo" for the purpose of the Convention. Protection of embryo in the biomedical research is asked for, in the Oviedo Convention.

Overall summary of the Qualitative Content Analysis (QCA) shows how the respondents commented on the destruction of human embryo:[25]

- Destruction of human embryo for research was considered unethical in general.

- Acceptable in limited circumstances. In-vitro creation of embryo for research purpose was not supported.

- Not accepted as massive therapeutic tools. Suggested alternative source of ESC.

- Embryo's rights (though limited) should still be respected.

- Good *scientific rationale, informed consent from donors and careful monitoring* were deemed essential.

XI. For ethical hSCR the clinical trial need to ensure certain formalities, e.g., informed consent, right to withdrawal, transparency and accountability (well documented procedure; redress by means of monetary compensation (in case of error committed by

[24] It actually indicates any research for the betterment of the embryo itself; NOT destroying it or extracting a *totipotent* blastomere cell for deriving the stem cells.
[25] *Supra* note 2.

the researcher)), post-trial care, etc.[26] Human Subject Protection (HSP) has to be taken very seriously in the process of development of human stem cell based inventions. Therefore, *conducting the safety and efficacy study properly is very important*.

XII. All actors and stakeholders do not perceive bioethics in the same way. It is a conglomerate of perceptions.[27] Bioethical principles will achieve better efficiency if they are *fluid* enough, *adaptable* to needs and circumstances and can be applied in the differing *contexts*.

XIII. Human right to "health care" and "right" based approach may increase access to health care in certain countries, which may allow access to the stem cell based therapy as well.[28] It may be guaranteed in the *constitutions* and be enforced through the *judicial system*. The international legal instruments like TRIPS Agreement may offer more concession.

The TRIPS framework ensures stronger IP protection and favors the inventor/patentee. The deal achieved through Doha Declaration 2001 for access to medicine is not flexible. Although it (Doha Declaration) helped access to essential medicines in some countries (for certain circumstances), a higher access to health care (e.g., for stem cell therapy) shall require more to be done. The compulsory licensing and authorization to local manufacturer is not a matter of free will of the country in need; the action has to comply with the criterion set by the TRIPS.

Overall summary of the Qualitative Content Analysis (QCA) shows how the respondents commented on the sources of finance and cost of the therapy:[29]

- Decision to accept the therapy and how it will be financed are separate issues.
- Acceptance contingent upon scientific proof of "treatment safety and efficacy."
- Varied sources of finance: personal expenses, provided by the State, insurance or in combination.
- Cost *expected to be reasonable*, if paid out of pocket.

XIV. The scenario of access to health care is different in different countries.[30] Therefore, the recommendation on access to therapy may be tailored differently for different countries.

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[26] See ch. 3.3.3 ETHICAL hSCR: INFORMED CONSENT, CLINICAL TRIAL, HUMAN SUBJECT PROTECTION AND RESPONDENTS' EXPERIENCE OF CONVENTIONAL MEDICATION FAILURE.
[27] See ch. 3.3 BIOETHICAL CONCERNS IN hSCR.
[28] See chaps. 3.4 ACCESS TO THERAPY: COMPULSORY LICENSING, RIGHT TO "HEALTH/HEALTH CARE" AND HEALTH CARE POLICY.
[29] *Supra* note 2.
[30] See ch. 3.4.1 ACCOMPLISHMENTS MADE IN THE COUNTRY CONTEXT.

In the USA, *ObamaCare* was introduced as a basic care coverage for the needy, the future of which is unknown. The European countries have social security or public health system to access the health care to a good extent. If they require co-pay and if it is slim, the accessibility will be higher in those countries. Small countries/economies do not attract generic's producer, and hence, they may enlarge their market size by merging with neighboring countries of similar economic/political/territorial status. A regulatory restructuring may be needed. It appears that the access to affordable care is limited in the USA. The key features of the health care facilities prevalent in the country context can be found in the following table:

Table 6.1 Health systems (features of health care facilities) in the country context

COUNTRY	KEY FEATURES OF THE HEALTH SYSTEMS	WORTH NOTICING
GERMANY	• Social Insurance • Compulsory Statutory Health Insurance • Private Insurance	"One third of the care providers (e.g. hospitals) are public; one third is not for profit and private, and one-third is for profit and private" (Simonet 2010, 473).
ITALY	National Health Service (*Servizio Sanitario Nazionale* (SSN))	• Twenty-one (21) Italian regions have differing standards of health care services; • "[S]ocial determinants can produce (different) inequalities inside different welfare systems." (Braggion, Campostrini, and Bertin 2013, 8).
LITHUANIA	Statutory Health Insurance	Disproportionate geographic distribution of family physician noticed (Buivydiene, Starkiene, and Smigelskas 2010, 262).
SPAIN	Health card from the Department of Social Security (*Tarjata Sanitaria Individual* (TSI))	• Reduction in health care budget; • Increased co-payment.
UNITED KINGDOM	• National Health Service (NHS) • Office of Health Ombudsman • Care Quality	• "[T]ax based national health system" (Lostao et al. 2014, 19); • Held in *Coombs v. North Dorset NHS PCT* (2013)[31] that it is possible for the patient to

[31] EWCA Civ 471, (2013) MHLO 35.

	Commission (CQC)	make additional payment for the expenses that are not the statutory responsibility of the NHS.
USA	The Affordable Care Act (ACA), 2010 (*ObamaCare*)	In the case of *National Federation of Independent Business, et al. v. Sebelius, Secretary of Health and Human Services, et al.* (2012),[32] twenty-six (26) States opposed the Affordable Care Act 2010.
CALIFORNIA	Medi-Cal Programme	
MASSACHUSETTS	• MassHealth • CarePlus • Free Care	
NEW JERSEY	• NJ FamilyCare • Individual Health Coverage (IHC)	
SOUTH DAKOTA	Healthcare.gov (Government's marketplace)	
TEXAS	• Rejected Medicaid expansion / *ObamaCare;* • Highest percentage of uninsured people among the American States.	

6.2 SUMMARY ON IPR ISSUES

The summary on IPR issues is drawn here from the discussion that took place in ch. 4. The Major Key Themes derived from the responses to questions related to IPR (question nos. 6, 7, 8, 9, 10, 12, 13) appear in ch. 4, as and when it deems appropriate to provide more insights into the discussion. The *interpretation of the Major Key Themes* derived from the responses to questions related to IPR can be found in Ch. 5. The o*verall summary of the QCA* of the IPR related questions appear in this sub-chapter.

Following are the summary analyses of both theoretical and empirical (qualitative) analysis on the IPR issues:

[32] 567 U.S. ___ (2012), 132 S.Ct 2566.

I. *Fate of US patent is unpredictable in Europe*.[33] WARF patent encompassing the destruction of human embryo was rejected by the Enlarged Board of Appeal (EBoA) of the European Patent Office (EPO) in G 0002/06[34] as the use of human embryo was considered as "commercialization" objectionable on the grounds of ""ordre public" or morality" enshrined in the Article 53(a) of the European Patent Convention (EPC), 1973.[35] WARF patents on ES cells derivation survived as US patents.[36] The recent US patent[37] of the Advanced Cell Technology, Inc[38] on the ES cell propagation from the *totipotent* and/or *pluripotent* blastomere cell derived from the pre-implantation stage IVF embryos are pending at EPO.[39] Will it not be an "*ordre public* or morality" issue for the EPO to use *totipotent* cells for ES cell derivation?[40] The CJEU's approach on patentability is not very predictable. CJEU has reinterpreted the *Brüstle*'s (2011)[41] exclusion in the *International Stem Cell Corporation* case (2014)[42] and opened the door for hpSC patent in Europe. The hESC patents by embryo destruction is excluded for the purpose of EP but hpSC patents are possible, according to the 2011 (*Brüstle* case) and 2014 (*International Stem Cell Corporation* case) decisions of the CJEU. iPSC was granted EP in 2011. The fate of EP for the rest of the hSCI[43] examined in this monograph is yet not known.

II. *The inventions are unlikely to be commercially exploited in some countries/states.*[44] Patent rejection in some countries is obvious, as the interpretation of the provisions on "ordre public" and/or morality is differently perceived by different patent offices. In some countries the inventions are unlikely to be sold and IP protected, whereas they shall remain patented in other countries.

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[33] See ch. 4.5.1 THE PREVAILING CIRCUMSTANCES IN hSCR AND PATENT: HOW DIVERGENT; 4.5.5 LIMITATION AND PROSPECTS OF THE US PATENTS FOR hSCI.

[34] Case No. G 0002/06. European Patent Office, *Search in the board of appeal decisions database*, *available at* http://www.epo.org/law-practice/case-law-appeals/recent/g060002ep1.html#q (last visited Dec. 14, 2014).

[35] European Patent Convention, Oct. 5, 1973, 13 I.L.M. 268, *available at* http://www.epo.org/law-practice/legal-texts/html/epc/1973/e/ar53.html (last visited Dec. 14, 2014).

[36] US Patent No. 6,200,806 (issued Mar. 13, 2001); US Patent No. 7,029,913 (issued Apr. 18, 2006); and the US Patent No. 7,442,548 (issued Oct. 28, 2008).

[37] US Patent No. 8,742,200 (issued June 3, 2014). United States Patent and Trademark Office, *USPTO Patent Full-Text and Image Database*, *available at* http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO2&Sect2=HITOFF&p=1&u=%2Fnetahtml%2FPTO%2Fsearch-bool.html&r=1&f=G&l=50&co1=AND&d=PTXT&s1=8,742,200&OS=8,742,200&RS=8,742,200 (last visited Nov. 12, 2014).

[38] Named as Ocata Therapeutics, Inc. since November 14, 2014.

[39] European Patent Office, *European Patent Register*, *available at* https://register.epo.org/application?number=EP12197502&tab=main (last visited Nov. 12, 2014).

[40] The *totipotent* cells and an embryo have the same/similar developmental potential.

[41] C-34/10, Judgment of the Court (Grand Chamber) 18 Oct. 2011, *available at* http://curia.europa.eu/juris/liste.jsf?language=en&num=C-34/10 (last visited July 25, 2014).

[42] Case C‑364/13, Judgment of the Court (Grand Chamber) 18 Dec. 2014, also *available at* http://curia.europa.eu/juris/document/document.jsf;jsessionid=9ea7d0f130de9c4121923b8f43769c42c1706a04f989.e34KaxiLc3eQc40LaxqMbN4ObheSe0?text=&docid=160936&pageIndex=0&doclang=EN&mode=lst&dir=&occ=first&part=1&cid=88991#Footnote* (last visited Dec. 22, 2014).

[43] NT-ESC and ESC from the blastomere cell of pre-implantation stage embryo.

[44] See chaps. 4.5 DIVERGENT PATENT FRAMEWORK FOR hSCI; 4.5.5 LIMITATION AND PROSPECTS OF THE US PATENTS FOR hSCI.

III. Commercial exploitation of certain patented inventions (patented in the USA as US patent) may not be possible in all US States.[45] The commercial exploitation of certain patented inventions (patented in the USA as US patent) may not be possible in all US States. As for example WARF patents were discussed in the chapter 4.5.5 on "LIMITATION AND PROSPECTS OF THE US PATENTS FOR hSCI." Those WARF patents (that derives hESC) may have problems in exploitation in the South Dakota (SD)[46] but can be freely commercially exploited in the other States, e.g., California, Massachusetts, New Jersey, etc., where the hSCR policy is liberal.

IV. *Ethical issues are causing divergence.*[47] Divergence in patent protection of hSCI between the USA and Europe is mainly caused by the European interpretation of the perceptions of "*ordre public* and/or morality." Therefore, all of the techniques detailed in chapter 3 are perfectly patentable in the United States. Most of them have already been issued several US patents (or applied for it). It is worth mentioning that, some of them cannot be useful patent in some of the US States that are very restrictive in human stem cell research, e.g., South Dakota.[48] hpSC patent is now possible in Europe. The CJEU in 2014 affirmed that the hpSC patents of International Stem Cell Corporation are not excluded from the patenting in Europe and the parthenogentically activated oocyte is not a "human embryo" for the purpose of exclusion from patenting.[49] But the restriction on derivation of ES cells seems to have retained its ethical constraints around the "embryo destruction" and "potential to live birth."

The major justification for the exclusion from patentable invention is cited as "*ordre public*" and/or "morality" in most of the legal texts revisited. Inventions encompassing/resulting/causing reproductive cloning and destruction of embryo are explicitly forbidden in many countries. Hence, they are excluded from being patented in those countries.

V. Divergence in patent framework of hSCI may cause/increase the mobility of patients and scientists and accelerate/trigger the health care inequalities.[50]

VI. *Private sector dominating the industry may result to higher cost of the transplant*.[51] The most advanced techniques of human stem cell research are patented by the corporations and autonomous institutions. It will have implication in the "access point." It may result to the higher cost of the transplant. The drug developers and downstream researchers developing disease specific application will have to pay royalties to these patentees, in

[45] See ch. 4.5.5 LIMITATION AND PROSPECTS OF THE US PATENTS FOR hSCI.
[46] As the SD laws/policies on hSCR is very restrictive.
[47] See ch. 4.5.1 THE PREVAILING CIRCUMSTANCES IN hSCR AND PATENT: HOW DIVERGENT.
[48] WARF US patents on ES cell derivation techniques cannot be commercially exploited both in South Dakota (SD) and Europe (as European Patent).
[49] *Supra* note 42.
[50] See ch. 4.5.6 IMPLICATIONS OF DIVERGENT PATENT FRAMEWORK.
[51] See ch. 4.4.1 PROPRIETARY NATURE OF THE HUMAN STEM CELL BASED INVENTION/INNOVATION.

addition to their own research and development effort and cost. In some cases, these assignees themselves are developing the drug product. Ultimately the patients will bear the expenses of these invisible "backyard costs" of the therapy. Since the industry is heavily influenced by private sector, the cost of the therapy using these patented inventions will be high and borne by the patients, unless they are covered by the mainstream health care providing channel of the particular State (through insurance or public hospitals).

VII. Regulatory Data Exclusivity (RDE) might be an additional layer of protection for hSCI.[52] Many of the transplant and disease specific applications will be in the market when the patent will be near to end of the term of protection. The patent owners may "resort to"/seek the protection of clinical test data and by which the tenure of monopoly will be further extended. The arrival of generic product in the market shall be delayed until the patent and the data exclusivity right both have expired. The data exclusivity right exists both in the US and EU in different length. The minimum protection called in TRIPS (Article 39(3)) for the "undisclosed test or other data" against "unfair commercial use" (to prevent unfair competition)[53] has been exercised towards extending the IP protection and literally creating a *double protection regime*, the implication of which will be obvious delay of arrival of the generic in the market. Therefore, the Bolar exception makes no significant impact in fostering access to medicine/treatment/health care. The opportunity to exercise the authority to allow use without authorization of the right holder is very limited.

VIII. *Patent litigation, Re-Examination and Opposition Proceedings may cause substantial obstacles for the inventions on its way to the clinic.*[54] Figure 4.4 shows the apparent reasons of the inventions encountering reexamination, post-grant proceedings and patent litigations. Figure 4.5 shows the breakthrough publications and issued patents (U.S. Patents) in SCNT and its neighboring techniques from 2004 to 2014. That sub-chapter also demonstrated the *slim differences among the inventions*. It will not be a surprise, if plenty of patent litigations, re-examination and opposition proceedings occur in the pipeline of industrial application of this emerging field of science. They may slower the pace of the therapy to reach the clinic. There also exists high possibility of "double patenting"[55] and "evergreening."

IX. Patent issued/granted by different patent offices have different impacts and carries different weight to the patent owners.[56] Some of the National Patents (NP) may not have

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[52] See ch. 4.4.2 REGULATORY DATA EXCLUSIVITY, BOLAR EXEMPTION AND COMPULSORY LICENSE.

[53] Agreement on Trade-Related Aspects of Intellectual Property Rights, Apr. 15, 1994, Marrakesh Agreement Establishing the World Trade Organization, Annex 1C, 1869 U.N.T.S. 299, 33 I.L.M. 1197 (1994) [hereinafter TRIPS Agreement].

[54] See ch. 4.4.3 CONTROVERSIES, SLIM DIFFERENCES AMONG INVENTIONS, FUTURE LEGAL COMPLICATIONS.

[55] The chance persists as some of the inventions by the same inventors/assignees in the same direction, have very narrow differences.

[56] See ch. 4.5.2 PATENT OFFICES (EPO, USPTO) AND FEES DIVERGENCE.

much value to the patent owner but those patents will continue to have higher value in the US and EU. The EU patents will be more valuable than an NP. The US patent cover larger single market than many other countries. Therefore, before seeking the patent, the applicant will calculate the "pre and post" grant costs of the patent and the return from the commercial exploitation of that patent in terms of profit.

X. Patent grant and renewal fees are different in different patent offices.[57] That may lead to adopting different "patent strategy" in different territory by the patent owner for the purpose of commercial exploitation of the invention. The patent fees (pre and post grant) being different at different IP offices, the cost of the patent and the return from the market will be a considerable factor to the patent seekers.

XI. Territoriality of the patent system and the mode of use of compulsory licenses by some countries may not encourage some of the companies to commercialize their products in certain countries.[58] This phenomenon cannot be avoided. More harmonization may be achieved among the blocks of the States, but they will be procedural uniformity, not achieving any uniform interpretation of patentable subject matter. The patent enforcement difficulties may remain largely in place.

XII. The Unitary Patent shall bring only the procedural simplification for getting patents in the EU Countries.[59] The prospective patentees can not try UP for inventions that are excluded under the current EU laws or excluded under the national laws of some EU countries. The patent seeker may try the classical European Patent's route and elect the individual States where the patent is obtainable for that particular invention. Therefore, the patents not qualified for UP, but eligible for patent (NP (National Patent)) in any of the European States may be applied, granted, enforced and challenged nationally. Therefore, the EU patent (Unitary Patent) and UPC will not bring harmonization in human stem cell patent landscape, particularly in the ethically contested matters.

XIII. PCT, US patent, EP, UP, NP all are offering different routes of granting the patent in different territories.[60] There is no "one patent system." From the procedural point of view, several patent systems co-exist. PCT and US patent exist in the USA. PCT, EP, UP and NP exist in the Europe. The new UP and UPC will bring procedural harmonization, once fully taken effect in the contracting States of the EU. But the substantive interpretation of patentability has not been changed by the unitary patent package. Therefore, the UPC will act according to the existing European laws. Therefore, the issues that raise questions on patentability in the Europe remain in the same situation for the UPC as well. There is no "international patent" and there is no international enforcement mechanism. Patent is a nationally granted right. Therefore, for the purpose of validity and enforcement of a patent right, the litigants have to proceed through the

[57] *Id.*
[58] See ch. 4.5.3 TERRITORIALITY OF PATENT SYSTEM AND THE ENFORCEMENT ISSUES.
[59] See ch. 4.5.4.1 EUROPEAN PATENT AND UNITARY PATENT PROTECTION.
[60] See ch. 4.5 DIVERGENT PATENT FRAMEWORK FOR hSCI.

national judicial system. The EP is a bunch of national patent. The PCT is a procedure to get multiple numbers of national patents in one click. UPC will be able to enforce patent right in the territories of EU that are contracting party to the agreement establishing the UPC. But large scale harmonization in "recognition and enforcement" of "foreign IP rights and foreign judgment" is not going to happen any time soon.

XIV. Patent office (USPTO in this example) either do not possess the capacity and means of "replicating" the invention to verify the claim or simply do not do it.[61] H. Bion Co., Ltd. (Seoul, South Korea) was assigned the United States Patent No. 8,647,872 on February 11, 2014 having scientist Woo Suk Hwang and others as inventors for "[h]uman embryonic stem cell line prepared by nuclear transfer of a human somatic cell into an enucleated human oocyte."[62] The patent is believed to have been granted on the inventions the publications of which were later retracted. It indicates that patent office (USPTO in this case) either do not possess the capacity and means of "replicating" the invention to verify the claim or simply do not do it. If this is a practice/situation in all patent offices, then it is a vital weakness in the patent granting process.

XV. Broad patent claim for the upstream inventions may block the downstream research, require licensing and raise the cost of the medicinal/drug products.[63] Early hSCIs are going to cover broad claims undoubtedly.

XVI. *Overall summary of the Qualitative Content Analysis (QCA) shows how the respondents commented on the Appropriateness of patent system for life sciences inventions/innovations:*[64]

- *Skepticism on the appropriateness of patent system* for life sciences inventions/innovations.
- Not supportive of evergreening of patent.
- While some supported stronger IPR if hSCI is protected as biotech inventions, many would like to see *a simpler IPR framework* due to ethical constraints, increasing litigations and oppositions.
- *More than 20-year term of protection thought to be affecting access to therapy in less developed countries* (LDCs and Developing). The hSCI should undergo similar regulatory approval process as pharmaceuticals.

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[61] See ch. 4.4.3 CONTROVERSIES, SLIM DIFFERENCES AMONG INVENTIONS, FUTURE LEGAL COMPLICATIONS.

[62] United States Patent and Trademark Office, *USPTO Patent Full-Text and Image Database*, *available at* http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=%2Fnetahtml%2FPTO%2Fsrchnum.htm&r=1&f=G&l=50&s1=8,647,872.PN.&OS=PN/8,647,872&RS=PN/8,647,872 (last visited Dec. 30, 2014).

[63] See ch. 4.4.2 REGULATORY DATA EXCLUSIVITY, BOLAR EXEMPTION AND COMPULSORY LICENSE.

[64] *Supra* note 2.

XVII. *Overall summary of the Qualitative Content Analysis (QCA) shows how the respondents commented on the "entitlement of IPR":*[65]

- Forms of entitlement of IPR: depending on funding source and contracts made. Researchers preferred to be acknowledged with moral rights only. Cell line donors deserve due compensation.

- A common concern over commercialization aspect of IP. *Reduced commercialization suggested for hSCI targeted to health care*.

- Legal obligations suggested not to be mandated, *should be enforced only in the right context*. Instead, *better transparency and proper utilization of public resources* deemed more pragmatic.

- A better *informed public* can make better decision and give useful feedback. *Drug pricing policy and rationale should be made more transparent to the consumers*. Civil society should have the legal instruments to voice against undue commercial exploitation.

XVIII. The most resorted course of IP protection for hSCI at this moment is the patent. Apart from raising other concerns about appropriateness of the patent system for hSCI, it has worries for the assignees as well. The time spent in clinical trial and regulatory approval will be lost from the term of protection.[66] But the regulatory data exclusivity right compensates that loss.[67] However, some countries including the United States allow the extension of the term of protection of the patent on grounds like time lost in regulatory approval (Miller 2012, 10).

XIX. The European Group on Ethics in Science and New Technologies to the European Commission in 2002 explored the alternatives to patent protection for hSCI and finally concluded by recommending to keep this branch of science within the patent system while making few suggestions regarding the patent system for it (EGE 2002, 81-82).

As an alternative to patent,[68] trade secret have certain difficulties. To name a few:

- The product can be reverse-engineered in some cases or the secrets can be revealed once the product is in the market.

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[65] *Supra* note 2.
[66] See ch. 4.3.3 INDUSTRIAL APPLICATION.
[67] See ch. 4.4.2 REGULATORY DATA EXCLUSIVITY, BOLAR EXEMPTION AND COMPULSORY LICENSE.
[68] See generally chaps. 4.4 PATENT RELATED CONCERNS; 4.4.2 REGULATORY DATA EXCLUSIVITY, BOLAR EXEMPTION AND COMPULSORY LICENSE.

- Ex-employees may disclose information, despite confidentiality agreement.
- Information considered secret may be published with the Court's proceedings. Therefore, the IPR owner will not be interested to enforce the trade secret rights in the Court.
- The term of protection for trade secret is not limited like other forms of IPR.
- The law on trade secret (or on preventing unfair competition) is not so developed in many countries.

Lastly, the *sui generis* protection will create more diversity.

CHAPTER 7:
CONCLUSION AND FURTHER RESEARCH

7.1 CONCLUSION

Comparative analysis of ethical and legal issues in hSCR in the select jurisdictions reveal that the divergent interpretation of ethical issues is resulting to different legal and policy atmosphere for the stem cell research and patenting hSCI. Ch. 3.2 "HUMAN STEM CELL RESEARCH: LEGAL LANDSCAPE" showed that legal purview of hSCR policies ranges from restrictive to liberal. The views of the respondents are also found to be vivid, i.e., ranges from restrictive to liberal.[1] Ch. 6.1 "SUMMARY OF ETHICAL AND LEGAL ANALYSIS" (I, VII, VIII, IX, X) reveals that there are differing degree of consent to different kinds of stem cell researches. Therefore, it can not be said that opting any particular approach, i.e., liberal or strict, is an ideal choice, since the "lack of uniform policies and differing opinions" exist in this field of science.

Based on the analysis made in the chaps. 2, 3, 5 and 6, the following conclusion may be drawn to answer the research question[2]:

- For ethical hSCR, strict monitoring will be required to ensure full compliance with the policies (reflective of people's choices) adopted.

- There is need to learn how to manage *plurality and diversity* of choices, *prioritize and contextualize* issues, and frame policies that have *fluidity and adaptability* in a given context.[3] It may be extremely difficult to implement.

Ch. 3.3.3 "ETHICAL hSCR: INFORMED CONSENT, CLINICAL TRIAL, HUMAN SUBJECT PROTECTION AND RESPONDENTS' EXPERIENCE OF CONVENTIONAL MEDICATION FAILURE" discussed what needs to be done for *ethical hSCR* during the *clinical trial and application*. Based on the analysis of ethical and legal issues done by the researcher,[4] it can be concluded that Clinical trial on human always shall need effective regulatory control in all the countries where they are conducted. There may be necessity of long term care for the participant/patient (by addressing the risk factors in application- tumorigenicity and immune rejection).[5]

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[1] See ch. 5.1 QUALITATIVE DATA ANALYSIS (for the interpretation of the Major Key Themes derived from the responses to question (on ethical and legal issues) nos. 1, 2, 3, 4, 5, 11).

[2] Ch. 1.3 THE RESEARCH QUESTIONS OF THE MONOGRAPH (II. What are the legal/ethical/bioethical issues in human Stem cell Research (hSCR) and what needs to be addressed for "ethical" hSCR?).

[3] See chaps. 3.3 BIOETHICAL CONCERNS IN hSCR; 6.1 SUMMARY OF ETHICAL AND LEGAL ANALYSIS (XII).

[4] See chaps. 3.3.3 ETHICAL hSCR: INFORMED CONSENT, CLINICAL TRIAL, HUMAN SUBJECT PROTECTION AND RESPONDENTS' EXPERIENCE OF CONVENTIONAL MEDICATION FAILURE; 6.1 SUMMARY OF ETHICAL AND LEGAL ANALYSIS (XI).

[5] See chaps. 3.1.2 HUMAN PLURIPOTENT STEM CELLS; 3.1.2.4 ARE THEY SUBSTITUTE OF EACH OTHER OR DIFFERENT FROM EACH OTHER?; 3.1.2.5 CLINICAL, ETHICAL AND LEGAL CONCERNS OVER THE iPSC.

Based on the qualitative analysis and the theoritical discussion done by the researcher,[6] the following conclusion relating to the IPR issues may be made to answer the research question[7]:

i. Certain changes in the patent system may improve the present situation;[8] or

ii. A new IP protection framework may be designed for the hSCI or IBMHO;[9] or

iii. Alternative IP protection (meaning only one should be opted; not multiple) may be exercised.[10]

The following proposals may be considered to bring *certain changes in the patent system*:

- In future, the technical interpretation of "industrial application" may take into account the "access to therapy" issues and introduce *a new requirement* (Accessibility Mode) for satisfying the "utility" / "industrial application".[11]

- It seems that the quality of patent may depend on good "search and examination". That may be a costly process, but with time, the standard has to be increased. The capability/expertise of the patent examiners will also have to be raised.[12]

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[6] Chaps. 5.1 QUALITATIVE DATA ANALYSIS (the interpretation of the Major Key Themes derived from the responses to question (on IPR issues) nos. 6, 7, 8, 9, 10, 12, 13); 4 ANALYSIS OF IPR ISSUES.

[7] Ch. 1.3 THE RESEARCH QUESTIONS OF THE MONOGRAPH (I. What is the best way to offer IP protection to "human Stem Cell based Inventions/Innovations" (hSCI) / "Inventions/Innovations that use Biological Materials of Human Origin" (IBMHO) that would ensure incentive for invention/innovation and allow wider access to therapies?).

[8] See ch. 6.2 SUMMARY ON IPR ISSUES (IV, V, VII, VIII, IX, X, XI, XIV, XV, XVI, XVII).

[9] See ch. 6.2 SUMMARY ON IPR ISSUES (XVI; XVII).

More empirical investigation shall be necessary to implement this proposal.

[10] See chaps. 4.4.2 REGULATORY DATA EXCLUSIVITY, BOLAR EXEMPTION AND COMPULSORY LICENSE; 6.2 SUMMARY ON IPR ISSUES (VII).
Dual protection exists in pharmaceutical inventions, i.e., patent and RDE right. Although RDE protects clinical test data, there may be information that are covered under an existing patent. There may be Patent, RDE and *a new IP protection framework* for the "inventions/innovations that use biological materials of human origin" / "human stem cell based inventions" / "regenerative medicine". But only one should be exercised; not multiple.

If this idea will become reality or not, will depend on the will of multiple actors.

[11] The commercialization channels of the invention will be scrutinized if that approach is taken seriously, while granting the patent. In the past, "utility or industrial application" has taken into account the feasibility of the invention from its technical potential and that approach has, in a way, favored the patentee only. In health care related inventions, a new approach in the interpretation of "industrial application" asking for the "accessibility mode" of the invention, may favor the patient population. The patent application may require an explanation on "how the researchers and general population will access/utilize the invention (to serve the 'utility' / 'industrial application' purpose)."

See Chaps. 4.3 PATENTABILITY REQUIREMENT FOR THE hSCI; 4.3.3 INDUSTRIAL APPLICATION.

[12] See chaps. 4.4.3 CONTROVERSIES, SLIM DIFFERENCES AMONG INVENTIONS, FUTURE LEGAL COMPLICATIONS; 6.2 SUMMARY ON IPR ISSUES (VIII; XIV).

- Heightening the "non-obviousness" standard will reduce the number of bad patents. Plenty of stem cell patents are challenged at Court over the lack of novelty and inventive steps.[13]

- Generics do not recover the entry cost from small markets, and hence, small countries that have small markets do not get cheaper medicine even after the patent expiration.[14] Small countries with similar economic circumstances can be merged with other neighboring small countries for the regulatory purposes and a *single market* can be created for those States.[15] Then the generic can be launched for the single market of multiple States. The wider single market will also reduce the frequency of parallel trade. The problem here is that the patent expires in different countries at different times. Exactly at which point of time the entry of generics will take place in that single market, have to be decided first. Therefore, this proposal is subject to the determination of the "term of protection" of the patent for that market.

- The provisions on compulsory licensing (use without authorization) in TRIPS may be relaxed and wider number of circumstances can be included, under which the unauthorized use by a country in desperate need of the treatment/therapy can be allowed/tolerated.[16]

Based on the qualitative analysis[17] and the theoritical discussion[18] done by the researcher, the following conclusion (for fostering the access to the stem cell based therapy) may be made to answer the research question[19]:

- Differentiated pricing of pharmaceutical products already exists. We need *affordable pricing* considering the income level of the people of the respective countries where the invention/innovation is being commercially exploited. The IP protection needs to respect the affordability issues involved in accessing the medicinal products.[20] Even co-payment with the insurance can be unaffordable to a higher number of patients. It is highly unlikely that the current patent system will offer such concessions.

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[13] See chaps. 4.3.1 NOVELTY IN hSCI; 4.3.2 INVENTIVE STEP/NON-OBVIOUSNESS; 4.4.3 CONTROVERSIES, SLIM DIFFERENCES AMONG INVENTIONS, FUTURE LEGAL COMPLICATIONS; 6.2 SUMMARY ON IPR ISSUES (VIII).

[14] See ch. 4.5.6 IMPLICATIONS OF DIVERGENT PATENT FRAMEWORK.

[15] See ch. 6.1 SUMMARY OF ETHICAL AND LEGAL ANALYSIS (XIV).

[16] See chaps. 3.4 ACCESS TO THERAPY: COMPULSORY LICENSING, RIGHT TO "HEALTH/HEALTH CARE" AND HEALTH CARE POLICY; 4.4.2 REGULATORY DATA EXCLUSIVITY, BOLAR EXEMPTION AND COMPULSORY LICENSE; 6.1 SUMMARY OF ETHICAL AND LEGAL ANALYSIS (XIII).

[17] Ch. 5.1 QUALITATIVE DATA ANALYSIS.

[18] See chaps. 3.4 ACCESS TO THERAPY: COMPULSORY LICENSING, RIGHT TO "HEALTH/HEALTH CARE" AND HEALTH CARE POLICY; 3.4.1 ACCOMPLISHMENTS MADE IN THE COUNTRY CONTEXT; 4.4 PATENT RELATED CONCERNS; 6.1 SUMMARY OF ETHICAL AND LEGAL ANALYSIS (XIII; XIV).

[19] *Supra* note 7.

[20] See chaps. 3.4 ACCESS TO THERAPY: COMPULSORY LICENSING, RIGHT TO "HEALTH/HEALTH CARE" AND HEALTH CARE POLICY; 4.4 PATENT RELATED CONCERNS.

- Irrespective of the economic status of the country, *efficacious* health care system, *pro-patient* regulatory policy, *sufficiently* allocated health care *budget*, *humanitarian* approach to IP protection of inventions having application in health care, may increase the access to the medicinal/drug products, if tailored for the circumstances and need of the population.[21]

- The right to health care can be guaranteed domestically.[22] The enforcement of such right will depend on the capability of the State.

- Already developed legal tools of international human rights laws can be enforced to allow the wider access to the therapy.[23] As an enforcement tool, human rights instruments are weaker than the trade agreements that protect stronger IP rights.

7.2 FURTHER RESEARCH AND EXTENSION OF THIS WORK

In future, studies can be done to reveal the correlation between "divergence in the patent framework" and the "stem cell tourism" / "price differences". As an impact of divergence in the patent framework, the treatment may be available in some specific countries. That may increase the health care tourism for stem cell based therapy. Further empirical investigations may be needed to reveal the implications of divergent patent framework on health care tourism. Divergent patent framework may not be directly responsible for the variation of medicinal/drug product's prices in the different countries. The prices of on-patent products are more expensive and the off-patent generics are usually cheaper. But many other factors are also linked to the price differentiation among the countries, such as demand-supply, market size, contribution of the Government and the insurance, ratio of co-pay with the insurance, Gross National Income (GNI) per capita, local manufacturing ability, parallel trade, Health Technology Assessment (HTA), health care needs and priorities of individual country, regulatory policy, tax policy, etc. An econometric analysis may reveal the relationship between divergent patent framework and the price differences.

[21] See chaps. 3.4.1 ACCOMPLISHMENTS MADE IN THE COUNTRY CONTEXT; 6.1 SUMMARY OF ETHICAL AND LEGAL ANALYSIS (XIII; XIV).
[22] See chaps. 3.4 ACCESS TO THERAPY: COMPULSORY LICENSING, RIGHT TO "HEALTH/HEALTH CARE" AND HEALTH CARE POLICY; 3.4.1 ACCOMPLISHMENTS MADE IN THE COUNTRY CONTEXT; 6.1 SUMMARY OF ETHICAL AND LEGAL ANALYSIS (XIII).
[23] See ch. 3.4 ACCESS TO THERAPY: COMPULSORY LICENSING, RIGHT TO "HEALTH/HEALTH CARE" AND HEALTH CARE POLICY.

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Appendix I: The Legal and Policy Framework

INTERNATIONAL LEVEL

Paris Convention for the Protection of Industrial Property 1883
World Health Organization Constitution 1946
Universal Declaration of Human Rights 1948
Convention on the Unification of Certain Points of Substantive Law on Patents for Invention (Strasbourg Convention) 1963
Declaration of Helsinki 1964
International Covenant on Economic, Social and Cultural Rights (ICESCR) 1966
Patent Cooperation Treaty (PCT) 1970
Strasbourg Agreement Concerning the International Patent Classification 1971
Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure 1977
WHO Declaration of Alma-Ata 1978
Vienna Declaration and Programme of Action Adopted by the World Conference on Human Rights in Vienna on 25 June 1993
Agreement on Trade-Related Aspects of Intellectual Property Rights 1994
Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine 1997
Additional Protocol to the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine, on the Prohibition of Cloning Human Beings 1998
Patent Law Treaty (PLT) 2000
Additional Protocol to the Convention on Human Rights and Biomedicine concerning Transplantation of Organs and Tissues of Human Origin 2002
Universal Declaration on Bioethics and Human Rights (UNESCO Declaration on Bioethics) 2005
Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research, Strasbourg 2005
United Nations Declarations on Human Cloning 2005
Treaty of Lisbon amending the Treaty on European Union and the Treaty establishing the European Community 2007
United Nations Resolution on Universal Health Coverage, 12 December 2012

EUROPEAN COMMUNITY LEVEL

Council of Europe (CoE) Convention for the Protection of Human Rights and Fundamental Freedoms 1950
Convention on Jurisdiction and the Enforcement of Judgments in Civil and Commercial Matters 1968
European Patent Convention 1973
Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the Legal Protection of Biotechnological Inventions
Charter of Fundamental Rights of the European Union 2000
Directive on the Enforcement of Intellectual Property Rights 2004
Directive 2004/23/EC on Human Tissues and Cells
Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community Code Relating to Medicinal Products for Human Use
Commission Directive 2005/28/EC of 8 April 2005 Laying Down Principles and Detailed Guidelines for Good Clinical Practice as Regards Investigational Medicinal Products for Human

Use, as well as the Requirements for Authorisation of the Manufacturing or Importation of Such Products
Consolidated Version of the Treaty on the Functioning of the European Union 2012
Regulation (EU) No 1215/2012 of the European Parliament and of the Council of 12 December 2012 on Jurisdiction and the Recognition and Enforcement of Judgments in Civil and Commercial Matters
Regulation (EU) No 1257/2012 of the European Parliament and of the Council of 17 December 2012 Implementing Enhanced Cooperation in the Area of the Creation of Unitary Patent Protection
The Agreement on a Unified Patent Court 2013
Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC

COUNTRY CONTEXT

GERMANY

Health Insurance Act 1883
Patent Law (enacted on 5 May, 1936, as amended upto 31 July, 2009)
Basic Law for the Federal Republic of Germany (Grundgesetz, GG) 1949
Hospital Financing Act 1972
Embryo Protection Act 1990
The SHI Modernization Act 2004
Health Care Reform Act 2007
Act of Quality and Security of Human Tissue and Cells 2007
Stem Cell Act 2002 and amendment of 2008 (Law on Protection of Embryos in Connection with Importation and use of Human Embryonic Stem Cells)
Medicinal Products Act 2009

ITALY

Constitution of the Italian Republic1948
Hospital Services Reform Act 1968
Patent Law (Royal Decree No. 1127 of June 29, 1939, as amended by Legislative Decree No. 198 of March 19, 1996)
Law No. 40, Regulation of Medically Assisted Reproduction 2004
Law No. 78 of 22 February 2006

LITHUANIA

Law on Patents 1994 (As amended upto 10 May 2007)
Law on the Health System 1998
Law on Ethics of Biomedical Research 2000
Oviedo Convention on Human Rights and Biomedicine
Additional Protocol to the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine, on the Prohibition of Cloning Human Beings
Law on Pharmacy 2008

SPAIN

The Spanish Constitution 1978

Law on Patents 1986
Oviedo Convention on Human Rights and Biomedicine
Additional Protocol to the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine, on the Prohibition of Cloning Human Beings
Law on Assisted Human Reproduction Procedures 2006
Law on Biomedical Research 2007

UNITED KINGDOM
The Patents Act 1977
Human Fertilisation and Embryology Act 1990 (as amended by the Human Fertilisation and Embryology Act 2008)
Human Rights Act 1998
Human Reproductive Cloning Act 2001
National Health Services Act 2006
Health and Social Care Act 2012[1]

THE USA
The United States Constitution, Article 1, Section 8, Clause 8
Consolidated Patent Laws
United States Code, Title 35: Patents
United States Code, Title 15 :The Sherman Antitrust Act
Consolidated Patent Rules: Title 37 - Code of Federal Regulations- Patents, Trademarks, and Copyrights
Manual of Patent Examining Procedure
Leahy–Smith America Invents Act 2011
American Inventor's Protection Act, 1999, amended by the Intellectual Property and High Technology Technical Amendments Act of 2002
Patent Business Goals 2000
NIH Grants Policy Statement, U.S. Department of Health and Human Services, National Institutes of Health, (Oct. 1, 2012)
Stem Cell Therapeutic and Research Act 2005
Stem Cell Therapeutic and Research Reauthorization Act 2010
Human Cloning Prohibition Act 2009[2] Stem Cell Research Advancement Act 2009[3]
Stem Cell Research Advancement Act 2011[4]
Ethical Stem Cell Research Tax Credit Act 2011[5]
Federal Food, Drug and Cosmetic Act 1938

[1] Royal Assent 27 March 2012; Not yet in force.
[2] Status: Referred to the Subcommittee on Crime, Terrorism, and Homeland Security.
[3] Status: Referred to the House Committee on Energy and Commerce.
[4] Status: Referred to the Subcommittee on Health.
[5] Status: Referred to the Committee on Finance.

Medical Practice Acts[6]
21 CFR 314.80: Postmarketing reporting of adverse drug experiences
Code of Federal Regulations, Title 21, Vol. 1, Revised as of April 1, 2012, Subpart B--Informed Consent of Human Subjects
Code of Federal Regulations, Title 45, Part 46, Protection of Human Subjects, Subpart A, Revised January 15, 2009, Effective July 14, 2009
National Research Act 1974
42 U.S. Code Chapter 6A - PUBLIC HEALTH SERVICE
Patient Protection and Affordable Care Act 2010
Health Care and Education Reconciliation Act 2010
Biologics Price Competition and Innovation Act 2009
Drug Price Competition and Patent Term Restoration Act 1984 (Hatch-Waxman Amendments)
US Federal Food, Drug, and Cosmetic Act, 21 U.S.C.§ 355 (2010)
American Recovery and Reinvestment Act 2009
American Inventors Protection Act (AIPA) 1999
Bayh Dole Regulations, 37 CFR § 401 (2013)
Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, April 18, 1979
The Nuremberg Code
WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects
International Ethical Guidelines for Biomedical Research Involving Human Subjects by Council for International Organizations of Medical Sciences CIOMS) and World Health Organization (WHO)
American Psychological Association (APA) Ethics Code
Food and Drug Administration Modernization Act 1997
Food and Drug Administration Amendments Act 2007

THE USA: STATE LEVEL

California
CALIFORNIA CONSTITUTION, Article 35: Medical Research, Ss. 1-5
California Health and Safety Code, Section 125292.10, Section 24185-24187
New Jersey
Senate Bill No. 1909
Massachusetts
Chapter 27 of the Acts of 2005, Act Enhancing Regenerative Medicine in the Commonwealth.
Texas
Texas Medical Board's_ Rules/ Regulations on '*Use of Investigational Agents'* _ CHAPTER 198. UNLICENSED PRACTICE, 22 TAC §§198.1 - 198.3
South Dakota
South Dakota Codified Laws, CHAPTER 34-14: MEDICAL RESEARCH

[6] All States have Medical Practice Act. The Federation of State Medical Boards (FSMB) issues guidelines for the physicians.

Appendix II: Questionnaire

The responses of the participants/respondents in this study shall be analyzed for the purpose of the Doctoral Study conducted by ARIF JAMIL, e-mail: **aaajamil@yahoo.com** (hereinafter referred to as Research Fellow), Erasmus Mundus Fellow (2012-2015) of **JOINT INTERNATIONAL DOCTORAL DEGREE IN LAW, SCIENCE AND TECHNOLOGY (LAST-JD)**. http://www.last-jd.eu. The information provided can be used/published by the Research Fellow and CIRSFID, University of Bologna; otherwise shall be considered confidential and the identity of the participants shall be kept anonymous, unless required to prove the authenticity of the study. The participants/respondents hereby consent to take part in the study.

Name (optional):
Age Group: (A: (less than, and 25), B: (26-30), C: (31-35), D: (36-40), E: (41-45), F: (46-50), G: (51-55), H :(56-60), I: (61-65), J: (more than 65))
Gender:
Current City, Country:
Profession/position:
& Category of respondent (*respondent can choose more than one category which would be appropriate to his/her background/profession/position*):

(a) Academic (please specify field):
(b) Ethicist/Bioethicist
(c) Judge
(d) Lawyer
(e) Patent Examiner
(f) Patient (Medical condition can be mentioned, but optional):
(g) Patient Advocate
(h) Physician/Doctor
(i) Researcher (please specify field):
(j) Scientist (Please specify field):

Note: It should be mentioned that you may respond according to your opinion, some answers are merely suggestions, and you may make specific remark, different from the suggested ones, if you think appropriate)

1. Do you bear any negative impression / any prejudice about human stem cell research?

(a) Yes
(b) No

If 'yes' Why? -

2. How do you perceive the terms 'embryo', 'human body' and 'human life'?

(a) They are same things and deserve the same rights.
(b) They are different forms of human being and deserve same rights.
(c) They are different entity, they have different status and they have different rights.

My answer is different from above. I think……

3. How do you see the act of destruction of human embryo for the purpose of research and invention/innovation?

(a) Unethical act, because it is against God's will (my religion does not allow it).
(b) Unethical act, because I consider embryo as human being or human body.
(c) Destruction for research and scientific experiments aimed at developing means to cure critical diseases can be allowed, despite the ethical issues divide opinions.
(d) Embryos are not human and if the destruction is a process that might bring medication for complicated and terminal diseases, I would not say that the act of destruction is unethical.
(e) Embryo at early stage is a different component from human being or human body. They are biological material of human origin and there is nothing unethical about its destruction.

My answer is different from above. I think……

4. Do you have experience of dealing with a situation when conventional medication or treatment could not help?
   (a) Yes, for myself
   (b) Yes, not for myself but for family members
   (c) Yes, for others
   (d) No
   (e) (*Please mentions here your experience in brief, if not covered by the options*) …….

5. Having a choice and at a critical stage of grave illness would you choose stem cell therapy for your family member, if it promises a cure (suppose already available as treatment)?
   (a) Yes, and it would be good if the State provides the expenses.
   (b) Yes, and willing to take it at personal expenses too, provided that I expect the costs of the treatment are reasonable.
   (c) Yes, and the insurance should cover it.
   (d) Yes (*If you want to mention a reason or circumstances other than mentioned already, you may write here*) ……..
   (e) No. (*If you want to mention a reason, you may write here*) …….

6. Do you think patent protection as it exists today is the best way to provide incentive to human stem cell based inventions/innovations?
   (a) Yes
   (b) No
   (c) No, because patent has embarked into too much complications and uncertainty of enforcement.
   (d) No, because it is inappropriate for rewarding inventions/innovations in life science.
   (e) No, because patented inventions are property of the patentee/assignee and it invokes exclusive commercialization.

(f) No, because patented human stem cell based invention/innovation is a form of commercialization of 'life'.

Why/other opinion:

7. Do you think that a new protection mechanism/framework can be / should be developed within the purview of intellectual property law (IPR), separate from patent, for the inventions/innovations that use biological materials of human origin and targeted to health care?

(a) Yes (can be)
(b) Yes (should be)
(c) No

Other opinion (please suggest)/ Why:

8. How many years of protection (term of protection for commercial exploitation) is appropriate for human stem cell based inventions/innovations?

(a) More than 20 years
(b) 20 years
(c) 15 years
(d) 10 years
(e) 5 years
(f) No protection

9. Which application of human embryo can be permitted according to your opinion?

(a) Commercial and industrial application for therapeutic purposes
(b) For research purposes
(c) For both the above
(d) None of the above

Others, please mention:

10. Who, according to your opinion, should be entitled to the intellectual property rights (IPR) of human stem cell based inventions/innovations?

(a) Scientist/Inventor
(b) Employer organization/University/Assignee
(c) **a** and **b** both
(d) State through its Department responsible for heath care;
(e) None of the above
(f) No one should own IPR of human stem cell based inventions/innovations.

Other (or please suggest, if your opinion is different):

11. Do you consider that the benefits of hESC (human Embryonic Stem Cell) research is more important than the risks and costs associated to it?

(a) Yes
(b) No

Any reason? -

12. Do you think legal obligation for issuing 'licenses on easy terms' or 'compulsory licenses' and 'technology transfer' can bring benefit to the patients by ensuring availability of medication/treatment at a reduced cost and may also serve as incentive for the IPR right owner of human stem cell based inventions/innovations at the same time?

(a) Yes
(b) Yes, but for the cost reduction the public health care sector has to be involved.
(c) Yes, cost reduction is possible if the licenses are issued in favor of local pharmaceutical companies/hospitals and therapies and medications are manufactured and produced locally.
(d) I think yes but I am not so sure
(e) No
(f) I hold different opinion such as (or you can mention your reason here) _____

13. Do you think *public opinion* should be sought and be given importance after the invention/innovation is put to the market for commercial exploitation, in order to measure the impacts of the IPR protected invention/innovation on the health care receiver?

(a) Yes
(b) Yes, and public opinion can be received online.
(c) No
(d) I have a specific opinion/suggestion about seeking *public opinion*. I think……

<u>Question regarding *familiarity* of the topic</u>

- How familiar you are with the questions asked in this questionnaire?

(a) Very familiar.
(b) Quite familiar but not all.
(c) Some were familiar and some were not so familiar.
(d) I could understand very few questions, not so familiar in general.
(e) Not familiar at all.

General information about patent:

Patent is granted by a State in favor of the patentee/assignee, empowering the owner (patentee/assignee) the right to exploit the invention commercially for the period called "term of protection" which is usually 20 years. Patent is granted in almost all fields of technologies, provided the inventions have to be **new**, **non-obvious** to the person skilled in the art **or** must have an **inventive step**, and shall have a commercial/**industrial application**.

Patenting (both process and product) inventions/innovations in 'life science' / 'biomedical research field' / 'evolutionary developmental biology' has existed for few decades. But this field of '**innovation**' has 'ethical concerns'. Countries are divided over the ethical issues relating to commercial application of inventions/innovations through patenting living objects, e.g., stem cells, genes etc.

Patent is an exclusive right. The owner alone can and is supposed to exploit the invention in the market. The price of a patented invention has risks to be monopoly price, i.e., higher than competition price. A perfectly organized legal setting should have a competition law/anti-trust law to look after the anti-competitive effect of dominant producer.

Appendix III: The Respondents

Email Address (Confidential Information)

The Questionnaire mentioned:
"The responses of the participants/respondents in this study shall be analyzed for the purpose of the Doctoral Study conducted by ARIF JAMIL, e-mail: aaajamil@yahoo.com (hereinafter referred to as Research Fellow), Erasmus Mundus Fellow (2012-2015) of JOINT INTERNATIONAL DOCTORAL DEGREE IN LAW, SCIENCE AND TECHNOLOGY (LAST-JD). http://www.last-jd.eu. The information provided can be used/published by the Research Fellow and CIRSFID, University of Bologna; otherwise shall be considered confidential and the identity of the participants shall be kept anonymous, unless required to prove the authenticity of the study. The participants/respondents hereby consent to take part in the study."

Therefore, I do not have permission to publish their email addresses. However, the email addresses were submitted to the LAST-JD Board with the first draft of this "Appendix." The list of the email address provided with the first draft of this file corresponds to the "Column # 1: Respondent Number" of the cumulative survey table.

Appendix IV: Questions' Design

For brevity reason, the content of this file (Appendix IV) is made available online. Please check the following link of the Dropbox.
https://www.dropbox.com/s/2cfjneed9yj5wo8/back%20matter%20appendix%20iv%20questions%E2%80%99%20designs%20link%20version.doc?dl=0

Appendix V: Qualitative Analysis (Qualitative Content Analysis (QCA))

ABBREVIATIONS:
Common Key Words (CKW)
Common Key Themes (CKT)
Unique Key Words (UKW)
Unique Key Themes (UKT)

Analyst of appendix VA is Arif Jamil[1] and analyst of appendix VB is Tania S. Bonny.[2] The goal of employing two analysts from two different background is to capture the different ways of interpreting the answers. Therefore, in some cases:

- *there were UKT but no UKW*
- *there were CKT, but no CKW*
- *there were CKW, but no CKT*
- *there were neither CKW, nor CKT, etc.*

Observations from both the analysts (developed in two separate appendices) were used to formulate "Common Key Themes (both analyst)" and "Unique Key Themes (one analyst)" which resulted to "Major Key Themes" and helped develop its interpretation.

Some of the words/phrases used/mentioned within quotation in the major key themes and their interpretations are the exact words/phrases used by the respondents.

1. Do you bear any negative impression / any prejudice about human stem cell research?

T12: "*No, even if "stem cell" is a very broad concept, I think that they represent a very promising therapeutic approach."*

Common Key Words (CKW): "even if"; "broad concept"; "promising"; "therapeutic".

Common Key Themes (both analyst): Promising area for therapy. Application oriented approach; HSCR invokes differing opinions.

Unique Key Words (UKW): "stem cell" is a very broad concept.

Unique Key Themes (one analyst (Tania)): Stem cell is a very broad concept (encompasses different components and associated ambiguity).

T20: "*Yes, because to obtain those cell, we must sacrifice with embryo. But, if those research use any method except killing human embryo so there is no problem."*

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[1] Ph.D. Research Fellow (2012-2015) in Bioethics and Biolaw, Erasmus Mundus Joint International Doctoral Degree in Law, Science and Technology (LAST-JD); LL.M. in IP.
[2] Ph.D. Research Fellow (2013 – Onward), Dept. of Environmental & Global Health, University of Florida, USA; Lecturer, Dept. of Microbiology, University of Dhaka, Bangladesh; M.Sc. in Microbiology.

CKW: "sacrifice with embryo", "any method except killing human embryo there is no problem".

Common Key Themes (both analyst): Against any stem cell research that involves destruction of human embryo. No objection if the research involves other methods than destruction of human embryo.

UKW: "killing human embryo".

Unique Key Themes (one analyst (AJ)): She expressed the process of "destruction" of embryo as 'killing."

T21: "*No, I consider it as any type of scientific research."*

CKW: "any type of scientific research".

Common Key Themes (both analyst): Human stem cell research is just like any other type of scientific research.

T24: "*Yes, to me it does not matter that-, for example, the embryos are produced in vitro – the bottom line is that an embryo is a living entity."*

CKW: "embryo is a living entity".

Common Key Themes (both analyst): Considers embryo as a living entity and he is against using embryo in research.

UKW: "Yes".

Unique Key Themes (one analyst (AJ)): The respondent is prejudiced about hSCR research.

T26: "*It depends on the type of stem cells used in the research. Somatic adult stem cell research as such generally raise no significant ethical or legal issue: I support this type of research.*

Embryonic stem cell research is highly controversial from ethical point of view: I am negative about it. Legal justification of such research needs some clarifications:

1) do human embryos possess any legal subjectivity? If no, what is a cogent legal argumentation which identify sound conditions for the transformation from res to persona? I am afraid that there are no sound explanation regarding the latter question – legislators feel uncomfortable facing that question and instead of it they tend to employ language of competing rights/interests.

2) is such type of research basic or applied science? If it is still a basic science issue, we already have several cell lines which can fully satisfy the need of biological material. In that case, it would be kind of "legal sacrifice" in favour of science. From my personal conversations with the researchers working in that field (they foresee that practical application could be expected in 30-50 years) I come to the conclusion, that this type of research is still a basic science. If it is so, it would be at least irresponsible to conduct clinical trials with humans without proper scientific knowledge, or to induce women to donate eggs at the expense of their health."

CKW: "type of stem cells", "embryonic stem cell research is controversial".

Common Key Themes (both analyst): Supports stem cell research if it uses somatic/ adult stem cell; He is against the hESC research for the ethical controversies.

UKW: "justification", "clarification", "legal subjectivity", "sound condition", "transformation from res to persona", "language of competition rights/interests", "basic or applied science" , "legal sacrifice", "basic science", "scientific knowledge", "women to donate eggs", "expense of their health".

Unique Key Themes (one analyst (AJ)): The respondent believes that no sound argumentation exist justifying/ illustrating the situation/ claim of the "transformation" of embryo from 'object' to 'person'. He thinks that the Legislators use the "language of competing rights/interests" instead of attending the first mentioned situation/question. According to his opinion, the hSCR is still a basic science, therefore, it would be "irresponsible act" to conduct clinical trial on humans and "induce" egg donation, "without" having "proper scientific knowledge".

UKW: "highly controversial from ethical point of view".

Unique Key Themes (one analyst (Tania)): He/she thinks some legal justifications of performing ESC research require clarifications regarding: a) what status embryo holds as compared to a human b) why and in what type of research they are utilized (basic/applied science). The respondent considers usage of human embryo in basic science research as irresponsible and calls this action 'legal sacrifice' in favor of science.

T30: "*Yes. I believe that specifically human embryonic stem cell research is politically and ethically controversial because it results in the destruction of a possible human life."*

CKW: "human embryonic stem cell research is politically and ethically controversial", "destruction of a possible human life".

Common Key Themes (both analyst): The respondent designates human embryo as a 'possible human life' and considers that hESC research is politically and ethically controversial because it results in the destruction of potential human life.

UKW: "Yes".

Unique Key Themes (one analyst (AJ)): The respondent is prejudiced about hSCR.

Major Key Themes derived from responses to question 1:

See 3.1.2.6.

Interpretation of the Major Key Themes derived from responses to question 1:

See Ch. 5.

Question 2: How do you perceive the terms 'embryo', 'human body' and 'human life'?

T7: "*an embryo does not have rights, given that it is not a human being."*

Common Key Words (both analyst): "embryo does not have rights, given that, it is not a human being".

Unique Key Themes (one analyst (AJ)): The respondent did not recognize any right that could be distinct to the embryo itself.

T9: "*I think an embryo at its earliest stage has no soul. It just a mass of undifferentiated cells. The is nothing "human" about it at this early stage. Whereas a human body and human life includes a soul."*

Common Key Words (both analyst): "embryo at earliest stage has no soul", "mass of undifferentiated cells", "nothing "human" about it at this early stage", "human body and human life includes a soul".

Common Key Themes (both analyst): Embryo at its earliest stage is a mass of undifferentiated cells.

Unique Key Themes (one analyst (Tania)): The respondent considers presence of 'soul' as a vital component of human body and human life. In the absence of 'soul' at this early stage, there is nothing 'human' about it.

Unique Key Themes (one analyst (AJ)): The respondent recognized the embryo as a cellular entity and recognized some kind of rights that are different from the human being.

T16: "*I think that term "embryo" lacks definition. It is unclear from which stage of development fertilized egg is deemed to be an embryo."*

Common Key Themes (both analyst): There is no consensus at which moment the growing organism shall be termed as "embryo". In her opinion, a conclusive definition of embryo does not exist.

UKT: There is absence of preciseness, conclusiveness and consensus on the definition of embryo.

Common Key Words (both analyst): "embryo lacks definition", "unclear", "stage of development".

Unique Key Themes (one analyst (AJ)): The respondent highlighted the absence of the consensus on the definition of the embryo. From her opinion, it appears that there exists an unspecified/ undefined period between the "fertilized egg" and the "embryos". In her opinion, the embryo deserves a "rights and status" different from the human.

UKT: There exists an unspecified/undefined period between the "fertilized egg" and the "embryos".

T22: "*I think……human body and life are separate from embryo.."*

CKT: The respondent considered human body, human life and embryo as distinct entities.

UKW: "separate".

UKT: The respondent draws a clear division between "embryo" and "human body and life". But he recognizes that the embryo deserves a distinct right.

T26: "*I think they all form a human being. Regarding the extent of the rights there should be a realistic approach: in my opinion human embryo should enjoy only those rights which are in his/her interests."*

CKW: "they all form a human being", "human embryo should enjoy only those rights which are in his/her interests".

CKT: The respondent considers embryo, human body and human life as integral parts that collectively form a human being.

UKT (Tania): The respondent considers embryo having a gender.

UKT (AJ): The respondent shows the "gradualist" approach here. To him they are same entity having different rights. His later response reveals that he treats embryo as human being.

T29: *"I think it depends on case and can't be used as a rule."*

CKW: "depends on case".

UKT (AJ): The respondent puts emphasis on the context, not on any preconceived notion. He indicates the prevalence of the contextually of perception and non-existence of a universality of perception.

T30: *"In my view, human embryo deserves special respect as a potential human being/possible human life; I would define it as the early stage of development of a human organism, however, I would not give to embryo completely the same moral and legal status as compared to humans, in terms of scientific research, abortion, etc."*

CKW: "special respect", "potential human", "early stage of development".

CKT: The respondent acknowledged a different and special status of the embryo from the human. She thought that the embryo is an organism of the earliest stage of human development.

UKT (Tania): The respondent considers human embryo as 'potential human being/ possible human life' and thus it deserves 'special respect'. She gives priority to the health, safety & well being of human being when it comes to usage of embryo in 'scientific research' and it's destruction in the case of 'abortion'.

UKT (AJ): She also takes a gradualist approach. In her opinion, they (embryo, human body and human life) are similar entity but have different rights.

Major Key Themes derived from responses to question 2:

See 3.1.2.6.

Interpretation of the Major Key themes derived from responses to question 2:

See Ch. 5.

Question 3: How do you see the act of destruction of human embryo for the purpose of research and invention/innovation?

T4: "*I think unethical but may be allowed in limited and in very serious disorder not as massive therapeutic tools…"*

CKW: "unethical", "may be allowed in limited and in very serious disorder".

UKT (Tania): The respondent finds the application unethical in general. However, he thinks that it is acceptable to employ embryo in limited circumstances e.g. the case of very serious disorder and at a limited scale. But he does not support using embryo as massive therapeutic tools.

UKT (AJ): Despite considering the embryo destruction unethical supporting the allowing embryo research for serious disorder or illness is not a contradictory position, rather a consequentialist/ utilitarian approach. He is considering the application in serious illness as more important than the sacrifice of ethics, but under special circumstances. To him, embryo and human being/ human body are the same things, deserving the same rights.

T6: "*As always, it is a balance between protecting the rights of the incapacitated embryo/fetus, and the value research can bring society and other individuals (originated from fetus's). But the individual rights should have priority."*

CKW: "balance", "rights of…embryo", "value research can bring", "individual right".

UKT (Tania): The respondent thinks that the embryo/fetus is incapacitated but still possesses some rights, although not to the same extent and magnitude as that of a fully developed human. He prefers a balance of rights and status of the embryo/fetus and the value of research that can benefit individuals and society. Still he/she prioritize individual rights, status and well-being over those of the embryo/fetus.

UKT (AJ): The respondent recognizes that the rights of the embryo need to be protected but to him the contribution of the research to the society and the individual is more important. The respondent demonstrates a mixed response of "pragmatic" and "utilitarian" approach. He stresses that a *"balance" is required between the conflicting interests of the entities, i.e., the "embryo" (which has the right to be protected) and the "society and individual"* (who will gain therapeutic benefits from the research). In the end, he thinks that the individual should have prior right to materialize the contribution of research and scientific experiments.

T12: "*Destruction for research aimed at developing means to cure critical disease should be allowed but only on Embryos that are anyway destined for destruction. I don't think it is ethical or correct to generate an in-vitro embryo in order to use it for subsequent researches."*

CKW: "should be allowed but only on Embryos that are anyway destined for destruction", "don't think it is ethical or correct to generate an in-vitro embryo".

CKT: The respondent supports only the use embryos in research that are redundant for clinical purposes (e.g. IVF). She considers the creation of *in-vitro* embryo exclusively for research purposes as unethical.

UKT (Tania): She also thinks that the research should be aimed at developing cure for critical diseases.

UKW (AJ): "Destruction for research", "developing means to cure critical disease".

UKT (AJ): This comment is also a pragmatic and moderate on the ethical perspectives in the debate around the embryo destruction for research. However, this approach can be said to be as one that does not compare the embryo with human being; rather the rationale or reasonableness of the action is viewed from the perspective of proportion and reality. The IVF redundant embryos are destined to be destroyed, so the use of those embryos do not create ethical outcry in the mind of the respondent. In the US, the IVF redundant embryos are used for hESC research.

T16: "*I think that term "embryo" lacks definition. It is unclear from which stage of development fertilized egg is deemed to be an embryo."*

CKW: "term 'embryo' lacks definition".

CKT: The respondent thinks that the term 'embryo' lacks definition.

UKW: "unclear", "stage of development".

UKT (AJ): The respondent highlighted the absence (scientific) of the precise moment when the fertilized entity shall be termed as embryo. She holds a pragmatic approach. She emphasized on the "stage of development".

T18: "*I suggest you to change the term "destruction" for the term "use".''*

CKW: "change the term "destruction" to "use"".

UKT (Tania): The word 'destruction' has a negative connotation.

UKT (AJ): This ideology of applying the term "use" is focused in the "application" of the embryo. Embryo's application is predominant in the mind of the respondent, and in that case, destruction of embryo would not create a significant ethical outcry for the process of production of the therapy. The "destruction" is viewed as "use", in other words as "application". He identifies embryo at early stage as a "biological material of human origin" and as a different component from the human being or human body. For him, "there is nothing unethical about its use." His suggestions for the replacement of the term "destruction" with the word "use" may have been intended to create a positive image of hSCR.

T21: "*This question has put me in a dilemma, my religious doesn't allow killing embryo in general but GOD allows research and I think according to that I can consider the necessity of the destruction of embryo i.e. is the destruction of the embryo a must to study a certain disease as to decide the method of treatment or the drugs have to be used to save others life or for any research purposes, may be my religion allows that (I'm not a religious scholar but if I'm the one who will do a research on embryo, I'll ask a religious man first). However, for me I don't consider it as a non-ethical situation as I measure it the same as clinical tests that may involve giving a patient a toxic or carcinogenic drug that may lead to his death, if I'm sure of its lethal or carcinogenic effect.''*

CKW: "dilemma", "God", "save others life".

CKT: The respondent has religious convictions.

UKW (Tania): "I'm one who will do a research on embryo".

UKT (Tania): The respondent's scientific decision is guided by her religious views. She seems to be contradicting herself though. She does not find it unethical when she is not practicing it herself; she compares embryo destruction for research purposes to clinical trials of therapeutic drugs. But if she is the one employing embryo for research purposes, she is undecided and needs religious support.

UKW (AJ): "measure".

UKT (AJ): There is a contradiction in perceiving the religious sense in the context of embryo destruction. In the end, the respondent is relying on the benefits, losses and application of the actions, which is a consequentialist approach. The respondent treats 'embryo' as equal entity as 'human being' but is willing to allow the destruction for finding cure to life saving treatments, because in her thoughts finding cure is more important than the embryo sacrifice. She is application oriented. Therefore, according to this approach, embryos are "human" but the destruction as an action is ethical if the future benefits are considered.

T22: "*There is no need for the destruction of the embryo because now people can harvest stem cells from cord blood-this a major misconception of the public.''*

CKW: "no need for the destruction of the embryo", "harvest stem cells from cord blood".

CKT: The respondent thinks that "cord blood" will substitute the need of embryo for the stem cell research. The respondent thinks that alternative sources are available; hence, there is no need of use of human embryo for research. The respondent considers embryo destruction is not required because his perception is that cord blood cells can provide the same types of stem cells.

T30: "*My answer is (c), however, with the certain conditions fulfilled like good scientific reason, informed consent from couples donating human embryos for research and careful research monitoring."*

CKW: : "conditions", "good scientific reason", "informed consent", "research monitoring".

CKT: The respondent supports destruction of embryo for research purpose in an attempt to developing cure for critical diseases but this action must pass through certain ethical barriers. She considers that fulfilling certain conditions like good scientific reason, informed consent from embryo donors and careful monitoring are critical. She is pragmatic too.

Major Key Themes derived from responses to question 3:

See Ch. 3.1.2.2.

Interpretation of the Major Key Themes derived from responses to question 3:

See Ch. 5.

4. Do you have experience of dealing with a situation when conventional medication or treatment could not help?

T6: "*As a medical professionals, you always at some point in time experience non-efficient medical treatment – this is just part of the trade (the variance of biological systems in individuals)."*

CKT: The respondent being a medical professional has the experience of limitation of the conventional medication or treatment and admits the inadequacy of medical treatment at some point.

CKW: "variance of biological systems in individuals".

UKW (AJ): "medical professional".

UKT (AJ): His reference of the differences and uniqueness of the individual's "biological system" points towards the necessity of personalized medicine/treatment.

UKW (Tania): "non-efficient medical treatment", "just part of the trade".

UKT (Tania): He considers that effectiveness of a particular medical treatment is highly subjective due to variability in the biological systems in individuals.

T9: *"Metaphysical science has a different approach where biological science fails."*

CKW: "Metaphysical science", "different approach".

CKT: Alternative approaches may exist; existence of limitation in the conventional approach of treatment taken in the biological science.

UKT (AJ): The respondent refers to alternative methods of treatment and care. In his mind, Metaphysical Science offers some solutions to the questions that cannot be solved through the

biological science. His observation can be interpreted to mean that alternative approaches may exist, when the limitation in the conventional approach of treatment taken in the biological science is obvious.

UKW (Tania): "biological science fails".

UKT (Tania): The respondent has experience dealing with medication failure in others. He thinks treatment based on biological science is often inadequate where metaphysical science may prove effective.

Major Key Themes derived from responses to question 4:
See Ch**.** 3.3.3.

Interpretation of the Major Key Themes derived from responses to question 4:

See Ch. 5.

5. Having a choice and at a critical stage of grave illness would you choose stem cell therapy for your family member, if it promises a cure (suppose already available as treatment)?

T4: *"Yes. Not worried about cost…but better if help comes from any source."*

CKW: "Not worried about cost", "any source".

CKT: The respondent is willing to bear the cost but prefers if the expense is covered by any source.

T6: *"PS: I think you need to divide the decision to accept of stem cell therapy vs. the decision of payment system (Denmark: socialized medicine through state; US: insurance and personal expenses)."*

UKW (AJ): "decision to accept of stem cell therapy", "decision of payment system".

UKT: Respondent thinks that the *decision to accept the stem cell therapy* and the *source that would meet the expenses of the therapy* are separate issues.

UKT (Tania): The respondent thinks that opting for stem cell therapy and the type of payment of system should be independent choices.

T10: *"No. (The majority of stem cell treatments being marketed today have no real basis in scientific evidence. There is no reason to expect that they work until adequate studies have been done.)"*

CKW: "real basis in scientific evidence", "until adequate studies".

UKT (Tania): The respondent considers that the majority of stem cell based therapy being marketed has no scientific evidence to be effective.

UKT (AJ): His rejection is subject to proof of the efficacy of the treatment.

T13: *"Yes and it would be good if the State provides the expenses, also considering that the State has to control such kind of treatment."*

UKW (AJ): "State provides the expenses", "State has to control such kind of treatment".

UKT (AJ): The respondent will opt for stem cell treatment but he expects that they are regulated by the State and the expenses are provided by the State too.

T17: *"Yes (If you want to mention a reason or circumstances other than mentioned already, you may write here)……Basically, all of the above: Yes. It would be good if the State provides the expenses or the insurance covers it; but if it doesn't cover them entirely or partially, then I would be willing to take it at personal expenses too, provided that I expect the costs of the treatment are reasonable."*

CKW: "State provides the expenses or the insurance covers it", "willing to take it at personal expenses too".

CKT: The respondent will choose stem cell treatments at personal expenses or financed through any source.

UKW (AJ): "I expect the costs of the treatment are reasonable".

UKT (AJ): Although willing to take the therapy at personal expense, she expects that the costs of the treatment are reasonable.

T19: *"Either a, b or c, depending of the health system in the country."*

CKW: "State provides the expenses", "the insurance covers it", "willing to take it at personal expenses too", "I expect the costs of the treatment are reasonable", "depending of the health system in the country".

CKT: The respondent will choose stem cell therapy and the way the expense will be covered will depend on the particular health system in a country.

T 26: *"Yes if it has already shown preliminary proved effect and relevant efficacy data is published in peer-reviewed journals."*

UKW (AJ): "proved effect", "published in peer-reviewed journals".

UKT (AJ): The respondent is willing to take the therapy, if the safety and efficacy of the therapy is proven and published in "peer-reviewed journals". He refrained from speaking about the expenses of the therapy.

Major Key Themes derived from responses to question 5:

See Ch. 3.4.

Interpretation of the Major Key Themes derived from responses to question 5:

See Ch. 5.

6. Do you think patent protection as it exists today is the best way to provide incentive to human stem cell based inventions/innovations?

T7: *"Yes. If biotech is involved in any way, patent rights alone may not be sufficient for adequate protection; I would propose the inclusion of ad hoc data exclusivity rights for biotech products/treatments. Regarding question 8, I would say that patent protection may not be suitable, however, the term of protection is indeed adequate, therefore, regulatory protection running on par with the patent term of 20 years would be the best option, going further than 20 years may cause market disruptions and would complicate access to medicines and treatment for less developed markets or people."*

CKW: "patent rights alone may not be sufficient for adequate protection", "inclusion of ad hoc data exclusivity rights".

CKT: The respondent thinks that existing patent protection may not be sufficient for adequate protection if stem cell inventions are commercialized as *biotechnology products*. In that case, he proposes the inclusion of "*ad hoc* data exclusivity rights" for biotech products. He is in favor of stronger IP rights.

UKW (Tania): Term of protection is adequate, market disruptions and complicate access to medicines and treatment, less developed markets or people.

UKT (Tania): However, he supports the existing term of protection for 20 years; going further than this would affect access to therapy for the patients in less developed countries.

T9: *"To say it's an invention or innovations or discovery in life science is totally inappropriate since life is already in existence. It is more appropriate to say realization and thus understanding and usage of the knowledge of this realization and understanding to better understand life science. Therefore how can any person claim patent protection on something which is already in existence."*

CKW: "inappropriate", "realization and understanding", "life is already in existence".

CKT: The respondent does not support the patent protection of inventions derived from living entities. Whatever has life cannot be patented; we can only understand and gather knowledge from it. The respondent finds patent protection as misfit for the inventions in life science.

T12: *"No, because patent has embarked into too much complications and uncertainty of enforcement. Especially in the field of hESCs, there are too many morality issues (see Brüstle legal battle). Litigations and oppositions are more and more frequent."*

CKW: "complications and uncertainty of enforcement", "morality issues", "litigations and oppositions".

CKT: The respondent considers that hESCs research has several ethical constraints. Litigations and oppositions are becoming more commonplace which makes it more difficult to protect these inventions.

UKT (AJ): She is suggesting a simpler IPR protection framework than patent.

T21: *"I think incentives can be ethical only (protecting the moral rights of the inventor) but not for commercialization purposes."*

CKW: "protecting the moral rights", "not for commercialization".

CKT: She supported IP protection in the form of "moral rights" only aka., right of recognition and integrity.

UKT (AJ): The respondent does not support the commercial feature of the IPR for life science inventions/innovations.

T22: *"Yes. Patents are finite in their length of time, most researchers discover things because of curiosity, and that is reduced by lawyers to something that can be owned or not, irrespective of the value of science in general or the altruism of people wanting to make a better world. This is something that lawyers and doctors seldom understand because they are motivated in the United States purely by profits."*

CKW: "researchers discover things because of curiosity".

UKW (Tania): "irrespective of the value of science in general or the altruism".

UKT (Tania): The respondent seems to believe that most researchers are driven purely by curiosity and altruism and not by financial incentives that are gained as a result of patent rights.

UKW (AJ): "lawyers and doctors seldom understand".

UKT (AJ): The respondent thinks that patent protection is ok in general (particularly it is fixed in the term of protection). He thinks that the stakeholders (doctors and lawyers) need to understand the noble purpose behind the innovation.

T26: *"I am not sure that patent protection in current shape is the best for inventions/innovations in life sciences – many concepts applied come from traditional fields of patent law, e.g. Chemistry inventions, which are little adaptable to inventions involving living organisms and thus may even have adverse social effect: consider recent Myriad case. If patent protects process inventions, I can't oppose them. However, I feel difficult in terms of novelty or inventive step to accept patenting of new therapeutic indications of the same technology."*

CKW: "little adaptable to inventions involving living organisms", "process inventions", "novelty or inventive step", "new therapeutic indications of the same technology".

UKT (AJ): The respondent is skeptical about the appropriateness of the patent system for life sciences but he did not say "no" to patent. The respondent also see it (patent) slightly misfit for protecting the living organism and raises concern regarding the possible adverse social effects. He has discontent about the examination of "novelty and inventive step" requirements of some of the patents. With changes of time, how patent is adaptable to newer inventions in life science is his question. He does not accept evergreening of patent, i.e., taking new patent for already known technology (for example, second medical application of known drugs).

UKT (Tania): The respondent is not sure if existing patent protection are appropriate and sufficient in the case of protecting new therapeutic products as an invention/innovation in life sciences. Traditional fields of patent law are hardly adaptable to inventions involving livings organisms and may create complicacy in enforcement. He/she, however, finds the existing framework okay in case of process patent.

T30: *"I am not sure, since early patenting is not only the incentive for companies to invest in research and development, but it also poses obstacles to collaboration and openness in research."*

CKW: "incentive", "obstacles".

CKT: To her, patent has two implications: 1. it's an incentive for research and development, and 2. it's a barrier for further research in connected fields of knowledge (limits the parallel and downstream research freedom).

Major Key Themes derived from responses to question 6:

See Ch. 4.4.

Interpretation of the Major Key Themes derived from responses to question 6:

See Ch. 5.

7. Do you think that a new protection mechanism/framework can be / should be developed within the purview of intellectual property law (IPR), separate from patent, for the inventions/innovations that use biological materials of human origin and targeted to health care?

T9: ***"****No, Intellectual property law should be used to protect new creations. Life science is NOT a new creation."*

CKW: "Intellectual property", "should be used to protect new creations", "Life science is NOT a new creation".

CKT: The respondent does not believe that a new creation can be made within the realm of life science. As he/she considers that IPR should be used to protect only new creations, human stem cell based inventions/innovations cannot be patented. The respondent is against the IPR protection of the life science innovations.

T10: *"I think that health care in general has been transformed, excessively and to the detriment of patients, into a business. People working in health care should have other priorities than making money."*

CKW: "health care", "transformed", "into a business".

CKT: Respondent does not support patent for many reasons.

UKW (Tania): "should have other priorities than making money".

UKT (Tania): He thinks that the various stakeholders of health care should be more pro-people, focusing more on how to provide affordable care and therapy to people rather than emphasizing on gaining financial incentives derived from patented technology.

UKT (AJ): He is in favor of reduced commercialization in health care sector, in general. The respondent is indifferent about a new protection framework, although thinks that patent in its current condition is not the best for providing incentive for hSCI. Therefore, be it a new protection framework, or existing patent, reduced commercialization is what the respondent expects as modification in the current IPR framework.

T21: *"No, I think no need to change the matter from research and development to protection which will be business and commercialization as this has to be done for the humanity and governments can*

fund this. I think here we need moral rights more that economical right (I mean to be protected as in copyright for the ethical concerns only)."

CKW: "humanity and governments can fund", "moral rights".

CKT: She does not support any protection framework that will have a commercial feature. In her opinion, the source of funding for research is the government's money. She thinks research targeted to healthcare is done for humanity. She will recognize the inventor but will not support the commercial features of the IPR or patent.

T22: *"I am not sure."*

CKW: "not sure".

CKT: The respondent is not sure if a new protection framework can be/should be developed.

Major Key Themes derived from responses to question 7:

See Ch. 4.4.

Interpretation of the Major Key Themes derived from responses to question 7:

See Ch. 5.

8. How many years of protection (term of protection for commercial exploitation) is appropriate for human stem cell based inventions/innovations?

T12: ***"****20 years or more, like pharmaceuticals this kind of inventions need to go through regulatory approvals."*

CKW: "regulatory approvals".

CKT: The respondent believes that 20 or more than 20 years is appropriate.

UKT (AJ): She indicates that the time spent in regulatory approval, if deducted from the term of protection, the IPR owner does not get enough time to exploit the invention commercially in the market. She does not support patent for the complications around its legal and ethical issues and she supports a new framework, but she suggests a longer term of protection.

UKT (Tania): The commercialization of these types of inventions/innovations should undergo similar type of scrutiny and obtain regulatory approvals to that of other pharmaceutical drugs.

T19: *"20 years, just because is the current protection period for patents."*

CKW: "current protection".

UKT (AJ): The respondents finds the current patent system is sufficient and so she suggested 20 years of protection.

Major Key Themes derived from responses to question 8:

See Ch. 4.4.2.

Interpretation of the Major Key Themes derived from responses to question 8:

See Ch. 5.

9. Which application of human embryo can be permitted according to your opinion?

T4: ***"****Only for therapeutic purpose + research purposes."*

CKW: "therapeutic purpose", "research purposes".

CKT: He will allow a very limited use of human embryo for research and innovation in cases of serious disorder, not for large scale commercial and industrial application (will allow limited therapeutic application).

T10: *"Academic/NPO/government development of therapeutics."*

CKW: "Academic/NPO/government".

CKT: Academic/NPO/government development of therapeutics.

UKT (Tania): The respondent supports development of therapeutics when they are conducted by Academic/NPO/government and not by commercial for-profit organizations.

UKT (AJ): The respondent also supported (suggested) development of therapeutics by using human embryo, when they are conducted by Academic/NPO/Government.

T12: *"For both the above provided that are only used Embryos that are anyway destined for destruction."*

CKW: "only used Embryos that are anyway destined for destruction".

CKT: The respondent supports both forms of application but only employing redundant embryos that are anyway destined for destruction, which indicates he/she does not support in vitro development of embryo and its deliberate destruction for the purpose of research and therapy.

T18: ***"****I suggest you to complete the answer option (b) with "For research purposes and treatments to third persons"."*

CKW: "For research purposes and treatments to third persons".

UKT (Tania): The respondent seems to advocate for application of human embryo in research and to derive customized therapy for specific group of ill patients requiring the therapy.

UKT (AJ): The respondent does not support the commercial and industrial application of the human embryo. He is against the propertization of IPR by patent. So he is inclined to allow the application of human embryo for research targeted to find cure or drug development but not through commercial channels.

T21: *"I think that the protection to be moral only (i.e. the discoverer must have been noticed as the discoverer for that new drug) as an ethical incentive to him."*

CKW: "moral only".

UKT (AJ): She is neither allowing the typical applications of the human embryo and nor suggesting any new. She only reiterated that she will recognize the inventor's name but with no commercial right attached to it.

T22: *"Human embryos are not necessary for stem cells, cord blood can be used to generate any kind of stem cells- this is a reductionist 1990s approach to asking about stem cell research. This will affect the way people feel about research, I think it is silly to use an embryo when you do not have to. Many people who think that embryos should not be used would agree to use cord blood."*

CKW: "cord blood".

CKT: The respondents believes that human embryo and cord blood are equivalent sources of any type of stem cells and hence there is no need to use embryo, in addition people who might object to application of embryo might not do so if the research involves cord blood instead of human embryo. He presumes that cord blood would invoke less or no ethical concern as opposed to using human embryo. He suggested to conduct stem cell research by using the cord blood, instead of human embryo.

Major Key Themes derived from responses to question 9:

See Ch. 3.1.2.6.

Interpretation of the Major Key Themes derived from responses to question 9:

See Ch. 5.

10. Who, according to your opinion, should be entitled to the intellectual property rights (IPR) of human stem cell based inventions/innovations?

T6: *"(c) + Regarding stem cell inventions, I don't see any different views when it comes down to ownership rights to an invention, and the related contract law (vis-à-vis an employer or contracted consultant)."*

CKW: "ownership rights," "contract law".

UKT (AJ): Given the fact that the respondent finds the current patent system adequate to offer incentives for hSCI, his response to this question is a consistent reaction. He supports the present way of owning the IPR, particularly patent. (In employer and employee setting, the owning of the patent by the employer organization/ university as "assignee" and taking the recognition of invention as "inventor" by the scientists, is a common practice and it depends on the contract between the employer and the employee. In some cases, the inventor is also seen as the assignee with the employer). Given the fact that the "assignee" is the owner of the patent and is entitled to the right to commercial exploitation, the respondent asserts the contractual arrangement as determining factor, i.e., who will own the IPR.

T11: *"I am a bit unsure on this, but when I read a book about Henrietta Lacks, I was empathic on her situation and I believed that at least she should have received money for the use of her cells."*

CKW: "Henrietta Lacks," "at least," "money," "use of her cells".

CKT: She believes that a person who donates his/her stem cell for research purpose may be entitled to some rights or at least should be financially compensated to some extent. The respondent thinks that the donor of cell line, if not included as the owner of IPR of the inventions from his/her biological sample, should receive a compensation.

UKT (**AJ):** The respondent is mentioning about a "just" compensation for commercially developing an invention from the samples of a research subject.

T18: *"I suggest you to complete the answer option (a) with "Scientist / Inventor and patients."*

CKW: "Scientist/Inventor and patients".

CKT: The respondent supports that both scientist/inventor and patients should be entitled to the intellectual property rights (IPR) of human stem cell based inventions/innovations

UKT (AJ): The respondent in his response to this questionnaire, does not support the current patent system for its propertization and commercialization aspect, endorses "no protection" as term of protection for commercial exploitation and finally endows the entitlement of the IPR to scientists, inventor and patients. Since he is not in favor of commercialization and propertisation, the recognition of the ownership in his sense seems to me a "moral right", not an economic right (as the moral right is only limited to the recognition, not extended to the commercial exploitation). The respondent here considers the philanthropic aspects, rather than the conventional reality of the drug development and behavior of the market.

T21: *"The scientist is the owner of the moral right with the funding organization that funds the research expenses."*

CKW: "scientist," "moral right," "funding organization," "research expenses".

CKT: The respondent considers the scientist as entitled to the moral right of invention along with the funding organization that supports the research.

T22: *"comments on option (b): Definitely not these vampires who capitalize on the work of the researcher and contribute zero intellectual thought-merely facilities for which they are paid by the grant!"*

CKW: "these," "contribute zero," "facilities," "grant".

UKT (Tania): The respondent seems extremely frustrated on the educational/research organizations where scientists strive to bring in governmental or nongovernmental funds in order to support research. His response clearly points to the extreme competition for securing funds and associated funding crisis in the US research institutions. A big proportion of this fund secured by an inventor is mandated to flow into the research institutions he/she is affiliated to, which is usually termed as Indirect Cost (IDC)(also known as Facilities or administrative rates). The university spends this amount to provide the administrative and infrastructural support to the inventors and academics. For example the current IDC rate of federally secured grant is 50% for conducting on-campus research at the University of Florida (source: http://research.ufl.edu/faculty-and-staff/proposal-development-submission/budgeting-information/fa-rates-idc.html). What it means is that 50% of the grant money brought in by an academic through fierce competition goes to the University by default, he/she has to plan the research based on the rest 50% of fund). This mandate is a serious pressure for an inventor trying to secure enough funds to carry out research in a timely manner and making due progress. But when a patent is

granted, it often includes both the scientist and the university as the assignee. The respondent does not support this current practice of ownership for the above mentioned reason, mostly prevalent in the US.

UKT (AJ): The respondent will award the IPR to the inventor/ scientist only. Additionally he thinks that the employer organization/ university makes no intellectual contribution to the hSCI and most of their expenses are covered by "grants". Merely for the facilities they provide to the researchers, they should not be awarded with the IPR of the hSCI.

T26: *"If a process invention was financed by public funds it would be reasonable to consider: a) joint (scientist/inventor and public) entitlement, b) the sponsor (public) of the research is free to transfer them to public domain"*

CKW: "financed by public funds," "scientist/inventor and public," "public domain".

UKT (AJ): The respondent see public as entitled to the IPR along with the scientist/ inventor, if the research is "financed by public funds." And eventually the invention should be in the public domain as the financing for the research was done with public money, according to his suggestion. In his approach, the respondent did not consider the private funding and investment in biomedical research. His response to this question is subject to the funding sources (if public funding is the source of research, then the entitlement should be this way).

Major Key Themes derived from responses to question 10:

See Ch. 4.4.1.

Interpretation of the Major Key Themes derived from responses to question 10:

See Ch. 5.

11. Do you consider that the benefits of hESC (human Embryonic Stem Cell) research is more important than the risks and costs associated to it?

T2: "*Yes, It can be proven beneficial in curing diseases."*

UKW (Tania): "Proven, beneficial in curing".

UKT (Tania): The respondent has the conviction that human embryonic stem cell research is promising and can lead to developing effective cure of many diseases.

UKW (AJ): "beneficial," "curing diseases".

UKT (AJ): She puts more emphasis on future therapeutic benefits.

T5: *"Yes, because it holds promise in curing many debilitating diseases and health complications. This sector also opens up option of customized treatment for very rare diseases with low frequency among population (who are capable of paying for the research and treatment)."*

CKW: "promise," "diseases," "customized treatment," "rare diseases".

CKT: The respondent believes that the benefits of human embryonic stem cell research outweigh the risks and cost associated with it, as this type of research has practical application in curing many

diseases which currently has no cure. Again they also seem promising for rare diseases where a group of afflicted patients can afford to pay for the research and therapy. The respondent favors the hESC research for the future therapeutic benefits and adds to this discussion its potential application in personalized medicine and rare diseases.

T7: *"Yes. I do not really notice any risks regarding its research, as for costs, I agree as long as economic and viability studies are made, if government money is being spent on the research."*

CKW: "economic and viability studies," "government money".

UKW (Tania): "*not really notice any risks regarding its research* ".

CKT: The respondent does not notice any inherent risk of stem cell research employing human embryo. However, when it comes to cost, he/she emphasizes on conducting economic and viability studies making sure that government money (i.e. public resources) spent is well justified and brings out fruitful outcome.

T9: *"Yes, The benefits of hESC research out weights the risk and costs associated to it many folds. hESC are non specialize and pluripotent thus being able to differentiate into almost any type of cells. This provides great potentials in medical treatments of wide conditions. Thus indirectly reducing risks and costs in other medical researches using different approaches. Finally reducing time and costs in other life science researches."*

CKW: "potentials in medical treatments," "reducing risks and costs in other medical researches".

CKT: The respondent believes that the non specialized and pluripotent nature of hESC make them an excellent candidate for potential therapeutic interventions on wide conditions. The benefits outweigh the risk and costs in hESC research as well as contemporary medical research applying other techniques and thus reducing time and costs of other life science researchers.

T12: *"Yes. But if controlled by and subject to a strict and harmonized regulation"*.

CKW: "strict and harmonized regulation."

CKT: The respondent considers that the benefits would be more than the risks and cost associated with it only if this type of research undergoes strict and harmonized regulation as to how these studies are conducted employing hESC.

T17: *"Yes. Mostly because the benefit will provide extension of those who are already living"*.

CKW: "extension," "already living".

CKT: The respondent considers that this type of research is beneficial mostly because of effective therapeutic interventions obtained down the road which help to prolong the life of those "who are already living." She indicates that the advantage may contribute the increase of life expectancy.

T21: *"As any type of scientific research I see it is so important even if I'm going to damage something in my research trip as to get more benefit for the society, life in future and public health."*

CKW: "scientific research," "benefit for the society," "public health".

CKT: The respondent believes that there are inherent risks and variable amount of costs associated with every kind of medical research and hESC research is no exception. If risking the embryo serves to

invent a useful therapy that can benefit human life, health and the overall society, the respondent thinks it is important to do so.

T22: *"No, Again, cord blood is OK, embryonic stem cell research is not necessary at all."*

CKW: "cord blood," "embryonic stem cell research not necessary".

CKT: The respondent considers stem cells derived from cord blood are equivalent in function and potency to that of hESC and there is absolutely no need to employ human embryo in this type of research.

T24: *"No, I am not in favour of stem cell research that deals with human embryos"*

CTW: "not in favour of stem cell research that deals with human embryos".

CKT: The respondent does not support any kind of stem cell research that involves destroying or putting the human embryo at risk. He seems to acknowledge the dignity and rights of human embryo in parallel to a fully developed human being.

T26: *"Again, I would like to emphasize the nature of the research (basic/applied). If we do not have sound data from basic science, any applied research which strives for potential cures of Alzheimer's, Parkinson's and whatever other diseases is irresponsible."*

CKW: "basic/applied" "sound data".

CKT: The respondent thinks that the results of basic science should be promising enough to warrant further applied research. He considers hESC as an applied research employing human embryo without having solid and convincing basic science research data. Therefore, he deems employing hESC as potential cures of Alzheimer's, Parkinson's and other diseases as irresponsible.

T29: *"Yes and No. It depends on price and time factor."*

CKW: "depends on price and time".

UKT (Tania): The respondent believes the benefits of hESC are contingent upon costs associated with research and affordability of the final therapy as well as the time required to bring the research outcome from laboratory to the clinic.

UKT (AJ): The respondent see this question as something the answer of which depends on the individual case and circumstances. He saw the risk and benefit of hESC research from the economic point of view.

T30: *"I consider the benefits of hESC research important, however it is hard to unequivocally determine the general risk-benefit ratio and the possible consequences of hESC research without discussing concrete scientific cases."*

CKW: "risk-benefit ratio," "concrete scientific cases".

CKT: Although the respondent considers hESC research as important but he/she has reservation to generalize the risks, benefits and possible consequences of every hESC research but instead believes each scientific cases would vary considerably on these parameters and deserves special scrutiny to determine the individual risk and benefit. The respondent reminds that the answer of this question depends on the 'context' and circumstances of each case; there is no universal approach to this issue.

Major Key Themes derived from responses to question 11:

See Ch. 3.1.2.6.

Interpretation of the Major Key Themes derived from responses to question 11:

See Ch. 5.

12. Do you think legal obligation for issuing 'licenses on easy terms' or 'compulsory licenses' and 'technology transfer' can bring benefit to the patients by ensuring availability of medication/ treatment at a reduced cost and may also serve as incentive for the IPR right owner of human stem cell based inventions/innovations at the same time?

T7: *"No + Perhaps in another country, but as for Mexico, the huge amounts of money being spent in political campaigns, useless programs and corruption simply invalidate the argument that patented drugs or treatments are too costly for the government to step in and subsidize the costs."*

CKW: "political campaigns," "corruption," "invalidate the argument".

UKW (AJ) : "another country".

CKT: The respondent raises the issue of the context of the country. He made reference of Mexico and raised the issues of waste of resources in corruption and unnecessary programs. He thinks that the high price of drugs may have been used just as an excuse to blame the patent for contributing to high costs. The respondents considers that issuing legal obligation in Mexico will not serve useful purpose because according to him public resources are wasted in various ways rather than being utilized for projects beneficial for the common people. He finds the cost of the drugs as not a valid argument for the government not being able to subsidize the costs. The respondent considers that transparency and proper utilization of public resources are keys to realizing these goals in Mexico instead of issuing any forms of legal obligation. He, however, thinks that these measures may be beneficial for other countries with different context.

T9*: "Scientists' researches should not be restricted by legal obligations. Scientists are obligated to Humanity. Researches are conducted to better understand life science processes and to apply their understanding for the betterment of Humanity."*

CKW: "obligated to Humanity," "understand life science processes".

UKT (AJ): The response can be summarized as follows:

- hSCI/life science inventions are not new and should not be IPR protected; and therefore,
- there should be no obligation is conducting the life science research.

T10: *"I think the entire system of restricting access to medical innovations based on IP rights is fundamentally flawed."*

CKW: "system of restricting access," "flawed".

UKT (Tania): The respondent does not support the protection of IPR for medical innovations because he/she considers that access to therapies/products borne out of medical innovations should not remain restricted but rather be made available to everyone.

UKT (AJ): The respondent indicates that there is need to make improvement in the IPR mechanism in order to facilitate access to the medication. It appears that he finds that there are some impediments caused by IPR in accessing the medical innovations and there are "flawed" systems in place, when it comes to inter-relations between the IPR and access to medications.

T21: *"I agree with the research using embryonic cell destruction as to find a drug from chemical or synthetic origin but I don't agree on making drug products from embryonic cell because that means the embryos will be attacked for commercial purposes."*

CKW: "drug from chemical or synthetic origin," "commercial purposes".

CKT: The respondent supports use and destruction of embryo only to find a drug downstream of the research that will be exclusively of chemical or synthetic origin. She does not support directly utilizing cell components of embryo in preparing the drugs since that would encourage large scale embryo destruction for commercial production of therapy.

T26: *"I am not sure that there should be considered an "obligation" on patent holder – I would rather remain on the "faculty" of public authorities to choose compulsory license. May be in the latter case the list of conditions for that should be more sophisticated and flexible"*

CKW: "public authorities," "sophisticated and flexible".

CKT: The respondent does not support mandating or imposing legal obligations on patent holder, rather he believes that public authorities should be judicious on enforcing it where appropriate based on sophisticated and flexible conditions.

Major Key Themes derived from responses to question 12:
See Ch. 3.4.

Interpretation of the Major Key Themes derived from responses to question 12:
See Ch. 5.

13. Do you think public opinion should be sought and be given importance after the invention/innovation is put to the market for commercial exploitation, in order to measure the impacts of the IPR protected invention/innovation on the health care receiver?

T9: *"I think it is pointless for seeking public opinion when the public in general is not well informed to return a qualify or quantifiable opinion."*

CKW: "not well informed".

CKT: The respondent considers that the public in general are not informed enough to give valuable feedback on the post marketing impacts of IPR protected invention/innovation. The respondent raises the issue of dissemination and availability of information to the public. He doubts that, as the public is "not well informed", they are not likely to make solid contribution through their responses.

UKT (Tania): He thinks that a common people cannot give constructive comment, opinion or suggestion irrespective of the fact that any person can be or potentially be a consumer/recipient of that therapy.

T10: *"I am not sure this would work particularly well..."*

CKW: "not sure this would work".

CKT: He is skeptical about this issue of consulting public. He does not think that seeking public opinion will make any difference. The respondent is doubtful if seeking public opinion is going to be an effective means to measure the post marketing impacts of IPR protected invention/innovation.

T15: *"I think only if enough controversy, i.e., obvious public outcry. Otherwise it is not necessary."*

CKW: "controversy, public outcry".

CKT: She indicates that, if there is any issues related to "ordre public and morality" (obvious public outcry) then public opinion can be sought, otherwise it's not important.

T19: *"No, but there should be a good information about this issue so the public can take decision after being properly informed."*

CKW: "properly informed".

CKT: She emphasized on informing public before making their choice. But there is no need to seek public opinion after the product is put to market, according to her. The respondent does not support the idea of seeking public opinions to measure the post marketing impacts. Rather she thinks that information should be made available to the consumers *a priori* so that they can learn more about the therapy and make informed decision whether or not to purchase and use it. But no emphasis is given on seeking feedback from a consumer who already used the therapy or response from a potential consumer regarding its access and affordability.

T21: *"if the drug is going to be done by the embryos of the citizen of the country so you've to take the public opinion in consideration because they are going to be one of the constituents of the drug and of course they have to know, but may be if the country is going to import it, you may find people not so angry as they aren't going to share in making the drug by their embryos (though I'm not with any of the IPR systems available now can protect it in my opinion other that the right of an author of a published research paper)."*

UKW (AJ) : "embryos of the citizen of the country," "constituents of the drug".

UKW (Tania): embryo source, imported drug, available IPR system.

UKT (Tania): He/she also thinks that the existing IPR framework cannot protect this kind of invention/innovation.

CKT: The respondent considers that the source of the embryo from which the invention/innovation is made is the most important or perhaps the only issue that may concern the general consumers. The common people of a particular country might not object towards an imported therapy if the embryo used isn't derived from their countrymen. He/she assumes embryo source is central to public interest and not access, affordability, safety or efficacy of the therapy (in case the therapy is developed from hESC).

T26: *"I think that civil society should have legal instruments to contest commercial exploitation via judicial procedure only."*

CKW: "civil society," "legal instruments," "judicial procedure".

CKT: The respondent thinks that civil society should have the legal instruments available so that they can seek only judicial help against undue commercial exploitation. He does not seem to find

independent public opinion very effective as a means to giving post marketing feedback or any positive or negative responses.

T29: *"I think Public opinion should already be received before commercialization."*

CKW: "before commercialization".

CKT: He suggests seeking public opinion prior to commercial exploitation.

UKT (Tania): I don't know what purpose it will serve though, in terms of the key aspects of therapy i.e. access, affordability, long term safety and efficacy. Drug pricing rationale and policy is never fully disclosed to the consumer, so what purpose might pre-marketing public response serve if they don't have any knowledge and decision making role in drug pricing?

Major Key Themes derived from responses to question 13:

See Ch. 4.4.

Interpretation of the Major Key Themes derived from responses to question 13:

See Ch. 5.

Summary of thematic analysis:

Overall summary of 13 questions and key points in simple language are inserted in ch. 6.

Appendix VA: Analyst AJ

For brevity reason, the content of this file (Appendix VA) is made available online. Please check the following link of the Dropbox.

https://www.dropbox.com/s/oe4k4szcwhtb01h/back%20matter%20appendix%20ixa%20analyst%20aj%20link%20version.doc?dl=0

Appendix VB: Analyst Tania

For brevity reason, the content of this file (Appendix VB) is made available online. Please check the following link of the Dropbox.

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