Tutors: Lars Bengtsson
Cécile Brokelind

Department of Business Administration
Master of European Affairs

Human Stem Cells

European National Innovation Systems and Patents

Felipe Polina

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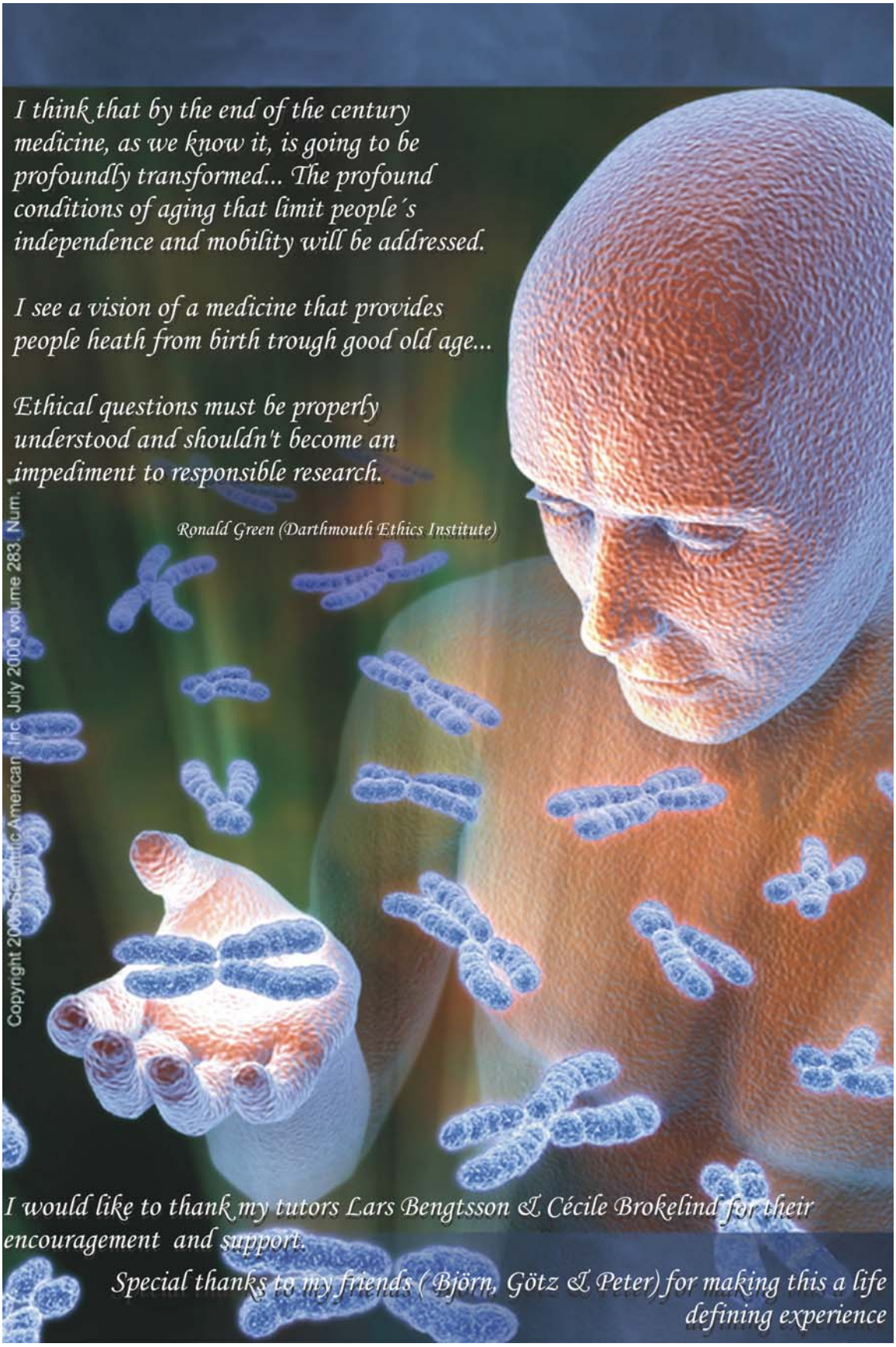

I think that by the end of the century medicine, as we know it, is going to be profoundly transformed... The profound conditions of aging that limit people´s independence and mobility will be addressed.
I see a vision of a medicine that provides people heath from birth trough good old age...
Ethical questions must be properly understood and shouldn't become an impediment to responsible research.
Ronald Green (Darthmouth Ethics Institute)
Copyright 2000 Scientific American, Inc. July 2000 volume 283, Num.
I would like to thank my tutors Lars Bengtsson & Cécile Brokelind for their encouragement and support.
Special thanks to my friends (Björn, Götz & Peter) for making this a life defining experience

1. Introduction

It's a windy autumn night at Stockholm and Laura is just arriving home from Karen's house (her best friend from school) and she just realized that there is no one home and she plans to take advantage of this by monopolising the TV and lying down on her favourite couch at her family room.

While Laura is doing this her parents and her little sister Jasmine are still at the hospital with Dr. Spencer trying to figure out which preventive therapy would be the most suitable for Jasmines from a foreseen congenital disorder that would make her loose her sight in a couple of years. This disease was found when Jasmine DNA was studied and profiled at her birth enabling Dr. Spencer and the genetics department of the hospital to set an action course in order to enhance Jasmines quality of life.

After two more hours and a couple of extra lab tests they decide to use some foetal stem cells, a revolutionary technique that has changed the way people live and overcome their illnesses and diseases.

Dr. Spencer decides to begin with the stem cell therapy in a week. After two sessions of therapy and a couple of evaluation follow up appointments Jasmine is released and now she is out of any risk from this degenerative disease.

As unreal, distant or taken out of a science fiction novel the previous story might sound this is the future of medicine in a couple of decades. Human stem cell research poses an unimaginable new horizon for human health, where prevention will be the key topic (especially with children) and gene replacement therapy and organs replacement surgeries will be the norm within developed countries.

This is a very exciting and promising time to be living at since nowadays the foundations for that future development of this technology are taken place by the different biotechnology innovation systems of countries around the world. In order to ensure that this future snapshot will come truth several key elements must work together (society, companies and laws). Unfortunately Europe as a whole unity is running behind other countries mainly because of the lack of an appropriate community legislation that gives general access to all Member States to a safe and harmonised human stem cells patent system.

So far the commission has managed not to answer the important question regarding the possibility to patent processes and products deriving from human stem cells in spite the fact that national laws from some Member States allow it, thus resulting on a disadvantageous position for most countries.

This later fact not only affects the MS human stem cell national innovation systems resulting in an inefficient allocation of resources which impact universities, employees, companies, researchers and ultimately the general public, but at the end of the day it affects the development of the European human stem cell innovation system position globally. It is imperative and of paramount consequences for European policy makers to give a position regarding this topic.

a. Purpose

The purpose of this paper is for the reader to realise how national innovation systems are deeply intertwined with the legal background of a country and to understand the processes that involves national innovation systems specifically regarding the stem cell / genetics research and how the need for specific community law must be considered targeting the stem cell patents. The legal part will try to answer: Why is it important given the actual state of the European stem cell national innovation systems for the European Commission to take a stand and tackle issues regarding the patenting of the human stem cell innovations? This is done from a country industry analysis (business approach) and then linking it with competition law from a community stand point of view (that tackles biotechnology issues). In order to achieve this the paper is divided into three separate analyses beginning with a theoretical background of general biotechnology / genetic terms that will enable the reader to have a general understanding of the importance of this kind or research (genetics / stem cell research). The chosen countries case studies exemplify very diverse economies and development perspective from the traditionally R&D intensive to the least and from the biggest countries in Europe to one of the smallest, thus giving cultural, legal, economic and scientific variety.

Following this part the core of the paper is presented by 4 case studies from different member states, this analysis is done from a national perspective encompassing firms, laws and financial resources; key factors that build up national innovation systems. The focus is to have a general mapping of where the selected member states position themselves regarding their stem cell innovation processes.
Finally the third part of the paper are the community legal issues that this kind of intensive R&D industry finds across the community and why it is important to have a very specific answer from the commission regarding stem cell practices since the community is lacking of general guidelines that allow all member states to have the same level of legal competitiveness.

b. Method

Since this thesis deals with social, industrial and legal issues it was only logical to begin by setting a general but strong theoretical foundation about the relevance of stem cell research in order to provide with a general understanding about why and how stem cell research is answering common questions giving clarification for the following parts that deal with the national innovation in stem cell research of 4 selected countries (case studies) and finally the legal part that concludes with the disparities of the laws (national and community wise) regarding human stem cells and biotechnology.
Most of the information used are primary sources (specially for the legal part) and secondary sources as well thought the paper.

1. Choice of literature

The 25 recommendations from the commission (2004) were the detonator for this thesis since they tackle with very important (ethical and human rights) points. Further more, socio-legal and comparative law literature were used extensible in order to achieve a sensible and sensitive approach that enabled the rest of the thesis to be supported. EC legislation, commission decisions, case law, journals and devoted scientific magazines have also been part of the literature used for this academic paper.

The choice of literature is an array of official sources such as national institutions of science of several Member States; community law compiled by: Commissions recommendations, Directives, Treaties and Case Law; scientific and some legal journals in order to have opinions different opinions and points of view of experts. Most of the sources consulted were online sources via online journals, online databases or directly through the institution website (taking advantage of the ELIN system provided by the Lund University Libraries)

The chosen countries to be studied have very different approaches and policies towards stem cell research and national innovation processes and show the socio-legal approach of different European member states to stem cell research and the link to their national innovation processes. It is also important to emphasise the heterogeneity of the countries economies beginning with the United Kingdom as a large country with high income, Germany which has been the financial engine of the Union and is as well a large country with high income, Spain with a less developed R&D industry but also a large country and economy but with a very different approach since it's a Latin European state, and last comes The Netherlands as an example of a small country with high income.

c. Delimitations

The focus of the thesis as mentioned previously is the comparison of biotech / stem cell innovation system from selected European countries and the necessity for the commission to answer crucial questions that have been avoided in the past and to have a harmonised community law that clearly approaches stem cell research issues in a very clear and precise way.

Evidently the impact of the national innovation systems and the legal structure of a country influences the base that enables the further development of the R&D structure (links between policy makers, legal systems, governmental agencies, universities, private firms and ultimately with the market). This paper will not take into consideration any other countries outside the EU for clarity and time reasons or any religious factor but only the ethical arguments of the commission and the European Court of Human Rights.

2. Scientific Background

a. Stem cells, a definition:

Stem cells are cells that can divide to produce either cells like themselves (self-renewal), or of one or several specific differentiated types. Stem cells are not yet fully differentiated and therefore can reconstitute one or several types of tissues.[1]

"Stem cells have the remarkable potential to develop into many different cell types in the body. Serving as a sort of repair system for the body, they can theoretically divide without limit to replenish other cells as long as the person or animal is still alive. When a stem cell divides, each new cell has the potential to either remain a stem cell or become another type of cell with a more specialized function, such as a muscle cell, a red blood cell, or a brain cell".[2]

b. Types of Stem Cells:

According to the Report On Human Embryonic Stem Cell Research "Different kinds of stem cells can be distinguished according to their potential to differentiate. They are progenitor, multipotent or pluripotent stem cells.

• Progenitor Stem Cells are those whose terminally differentiated progeny consist of a single cell type only. For instance, epidermal stem cells or spermatogonial[3] stem cells can differentiate respectively into only keratinocyte[4] and spermatozoa.

• Multipotent Stem Cells are those which can give rise to several terminally differentiated cell types constituting a specific tissue or organ. Examples are skin stem cells which give rise to epidermal cells, sebaceous glands and hair follicles or haematopoietic stem cells, which give rise to all the diverse blood cells (erythrocytes, lymphocytes, antibody-producing cells and so on), and neural stem cells, which give rise to all

[1] McLaren Anne, Hermerén Göran. Ethical Aspects of Human Stem Cell Research and Use 14 Nov. 2000, Pg 3 Opinion of the European Group on Ethics In Science and New Technologies to the European Commission

[2] The Official National Institute of Health Resource for Stem Cell Research. 2005, Maryland USA http://stemcells.nih.gov/staticresources/info/basics/StemCellBasics.pdf

[3] Any of the cells of the gonads in male organisms that are the progenitors of spermatocytes. Also called *spermatoblast*. (The American Heritage® Stedman's Medical Dictionary 2002 by Houghton Mifflin Company.)

[4] An epidermal cell that produces keratin. (The American Heritage® Stedman's Medical Dictionary 2002 by Houghton Mifflin Company.)

the cell types in the nervous system, including glia (sheath cells), and the many different types of neurons. (Both multipotent and progenitor stem cells may persist through life allowing the foetus to form tissue and organs and in the adult to replenish tissue whose cells have a limited life span like skin, intestinal and haematopoietic stem cells. Without these cells in our body we would dye due to lack of tissue regeneration).

• Pluripotent Stem Cells are able to give rise to all different cell types *in vitro* Nevertheless, they cannot on their own form an embryo. Pluripotent stem cells, which are isolated from primordial germ cells in the foetus, are called: embryonic germ cells ("EG cells"). Those stem cells, which are isolated from the inner cell mass of a blastocyst[5] -stage embryo, are called: embryonic stem cells ("ES cells")." (These kind of cells do not occur naturally in the body, which distinguishes them from the two previous ones)[6]
Please refer to annexe "***a"*** for further understanding about the differentiation process.

c. Where can stem cells be found?

"Scientists primarily work with three kinds of stem cells from humans: embryonic stem cells, foetal origin stem cells and adult stem cells. The first kinds of stem cells are derived from embryos that develop from eggs that have been fertilized in vitro and then donated for research purposes with informed consent of the donors. They are *not* derived from eggs fertilized in a woman's body. The embryos from which human embryonic stem cells are derived are typically four or five days old and are a hollow microscopic ball of cells called the blastocyst.
Stem cells of foetal origin can be retrieved from the umbilical cord blood (haematopoietic stem cells) and the adult stem cells. Finally adult stem cells have been identified in many organs and tissues. One important point to understand about adult stem cells is that there are a very small number of stem cells in each tissue. The adult tissues reported to contain stem cells include brain, bone marrow, peripheral blood, blood vessels, skeletal muscle, skin and liver." [7]

d. Importance of stem cell research:

[5] The modified blastula stage of mammalian embryos, consisting of the inner cell mass and a thin trophoblast layer enclosing the blastocoel. Also called *blastodermic vesicle*. (The American Heritage® Stedman's Medical Dictionary 2002 by Houghton Mifflin Company.)
[6] McLaren Anne, Hermerén Göran. Ethical Aspects of Human Stem Cell Research and Use 14 Nov. 2000, Pg 3 Opinion of the European Group on Ethics In Science and New Technologies to the European Commission
[7] McLaren Anne, Hermerén Göran. Ethical Aspects of Human Stem Cell Research and Use 14 Nov. 2000, Pg 3 Opinion of the European Group on Ethics In Science and New Technologies to the European Commission
The Official National Institute of Health Resource for Stem Cell Research. 2005, Maryland USA
http://stemcells.nih.gov/staticresources/info/basics/StemCellBasics.pdf

"Embryonic stem cells are of great interest to medicine and science because of their ability to develop into virtually any other cell made by the human body. In theory, if stem cells can be grown and their development directed in culture, it would be possible to grow cells of medical importance such as bone marrow, neural tissue or muscle.

The first potential applications of human embryonic stem cell technology may be in the area of drug discovery. The ability to grow pure populations of specific cell types offers a proving ground for chemical compounds that may have medical importance. Treating specific cell types with chemicals and measuring their response offers a short-cut to sort out chemicals that can be used to treat the diseases that involve those specific cell types. Stem cell technology, therefore, would permit the rapid screening of hundreds of thousands of chemicals that must now be tested through much more time-consuming processes."[8]

Some examples of potential treatment include diseases like juvenile onset diabetes mellitus and Parkinson's disease (replacing the dopamine-producing cells in the brains of Parkinson's patients) occurs because of defects in one of just a few cells types. "Replacing faulty cells with healthy ones offers hope of lifelong treatment. Similarly, failing hearts and other organs, in theory, could be shored up by injecting healthy cells to replace damaged or diseased cells.[9] As mention previously stem cells therapy will literally change the way we live and heal since no more conventional drugs will be necessary (why to cure when you can get a brand new organ?) not only our lives will be changed but the whole traditional pharmaceutical industry would be forced to shift.

[8] The Biotech Journal 2004,What's So Great About Embryonic Stem Cells?
http://www.biotechjournal.com/Journal/July2004/embryonicstemcells.pdf

[9] McLaren Anne, Hermerén Göran. Ethical Aspects of Human Stem Cell Research and Use 14 Nov. 2000, Pg 3 Opinion of the European Group on Ethics In Science and New Technologies to the European Commission
The Official National Institute of Health Resource for Stem Cell Research. 2005, Maryland USA
http://stemcells.nih.gov/staticresources/info/basics/StemCellBasics.pdf

3. National Innovation Systems

a. Definition

The OECD defines the national innovation systems as the "**flows of technology and information** among people, enterprises and institutions which are key to the innovative process. Innovation and technology development are the result of a complex set of relationships among actors in the system, which includes enterprises, universities and government research institutes. For policy-makers, an understanding of the national innovation system can help identify leverage points for enhancing innovative performance and overall competitiveness. It can assist in pinpointing mismatches within the system, both among institutions and in relation to government policies, which can thwart technology development and innovation. Policies which seek to improve networking among the actors and institutions in the system and which aim at enhancing the innovative capacity of firms, particularly their ability to identify and absorb technologies, are most valuable in this context."[10]

In the national innovation system approach, "innovative activity is usually analyzed in a broader sense instead of focusing solely on the number of introduced product and process innovations in a country, it encompasses also research and development efforts by business firms and public actors as well as the determinants of innovation like, for instance, learning processes, incentive mechanisms or the availability of skilled labour."[11]

In order to understand a national innovation system it is paramount to understand how technical advance occurs in the modern world, and they key processes and institutions involved such as R&D facilities, scientists and engineers trained by universities and attached to business firms, universities, government agencies and policy makers; are the principle vehicles through which technological advance proceeds. Figure a (below) summarizes how the flow of these core knowledge factors studied in this paper:

Figure a: Core knowledge flows in national innovation systems

Type of Knowledge flow	**Main Indicator**

[10] Organisation for Economic Co-Operation and Development. 1997 National Innovation Systems http://www.oecd.org/dataoecd/35/56/2101733.pdf

[11] Markus Balzat & Horst Hanusch, 2003. Recent Trends in the Research on National Innovation Systems, Volkswirtschaftliche Diskussionsreihe 254, Universität Augsburg, Institut für Volkswirtschaftliche http://www.wiwi.uni-augsburg.de/vwl/institut/paper/254.pdf

Industry alliances	
Industry/university interactions	
Co-operative industry/University R&D Industry/University financing	This will be assumed by the interaction between universities or research centres and by spin-off companies (mainly in the UK)
Industry/research institute interactions	
Co-operative industry/Institute R&D Industry/Institute financing	This indicator is mildly taken into account specially in Germany and The Netherlands

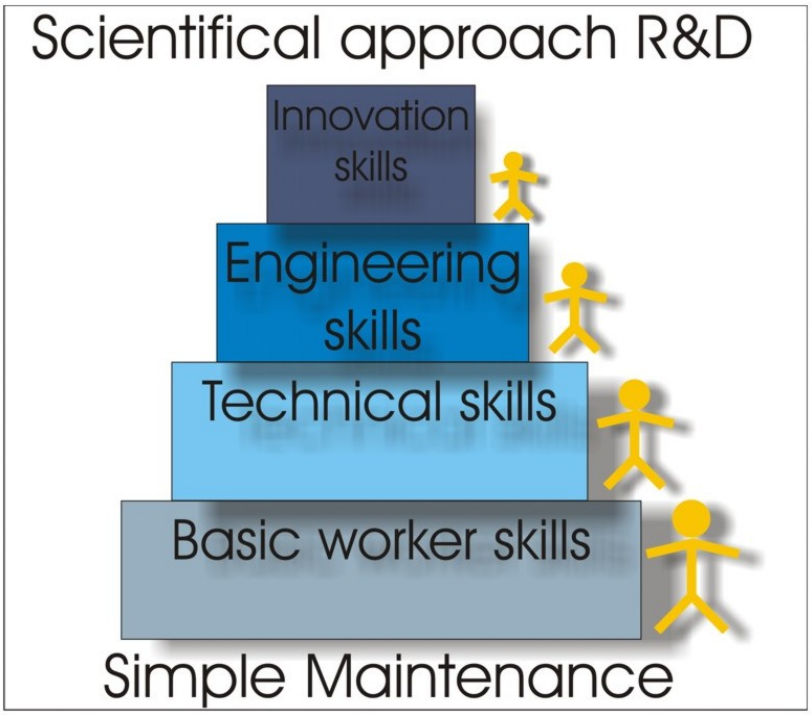
b. Background

As Nelson 1993 mentions a National Innovation System is a system that supports the ability/capacity of a country to innovate – especially to adapt and create science and technologies for economic and societal use. There is a clear sense of national technology that might be called "technonationalism"[12] which is a mix of the different technological abilities of the companies of a specific country, but certainly this is not the only factor to take into consideration when talking about national innovation systems:

"People: Linking and enabling knowledge, education, training, entrepreneurship. (The following chart explains how based within a need from human capacity the NIS build up from basic operators all the way to develop a R&D process.

As the following chart explains in a very simple but graphical way how education and training are a key element for the build up of NIS from a human perspective. The more labour intensive a job is the more less-qualified workers are needed and as soon as workers are trained and educated they develop technical skills which allow them to continue up the NIS ladder; furthermore, if more formal education is given within the appropriate environment engineering skills will be developed and finally the last step is to achieve a scientific R&D approach which requires the best trained and educated free-minded people. As noted the closer to the R&D processes the less people are required.

[12] Nelson R. Richard , 1993. National Innovation Systems. Oxford Univesity Press New York



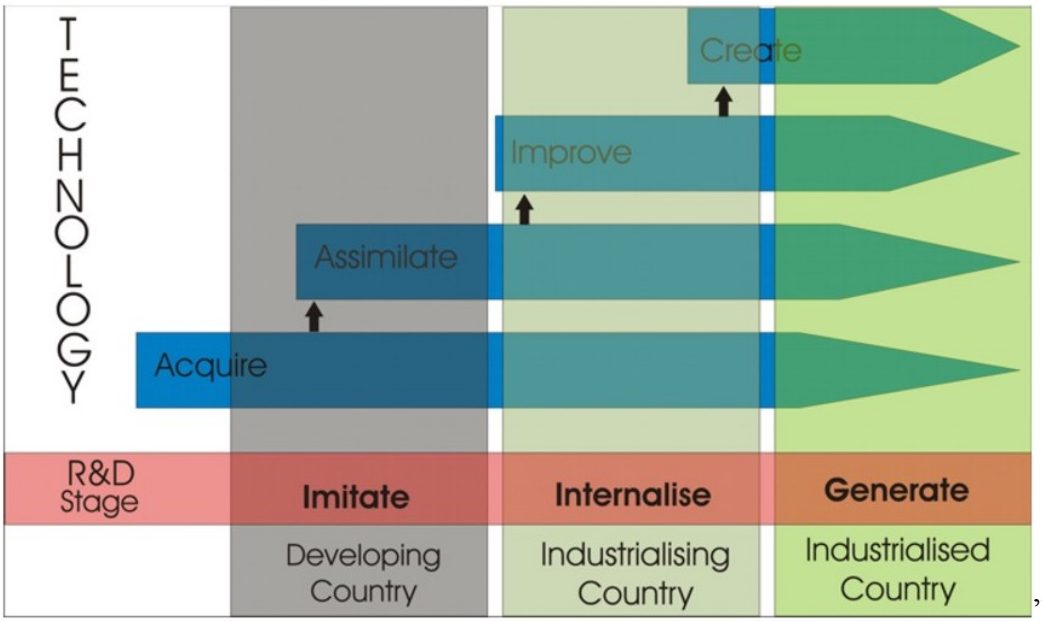
Policy environment: Focusing in under-funded areas, promoting new business opportunities, linking universities with the private sector, improving policies

Infrastructure: Take advantage of existing networks with institutions, research centres and universities, finances and funding.

Institutions: This push and pull process that institutions must do where the government is an important catalyst.

Political will: This is one of the most important factors and key elements that lobbyist must push forward since without political will from politicians and law makers the whole process could be stalled.

The following is a typical example of how a NIS works and is created from 3 different perspectives (depending on the development stage that the country is situated). The process is quite comprehensive and self explanatory where it begins by the acquisition of proven systems by imitation and then escalates to the assimilation of these innovation or discoveries, then it goes further to improve the previously imitated and assimilated innovation and finally in the most develop state it creates new knowledge, processes and products within such innovation system.



„[13]

4. European Biotechnology Innovation System

"Innovative performance is both a measure and a key component in national competitiveness and economic performance. In general, competitiveness can relate to three areas: currently produced goods and services; productivity in commercial flows; and competitive potential. "Sustained competitiveness depends upon the continual development of new and improved products, processes and services, and the transfer of know-how and technology between and within the actors of the "national system of innovation". Such 'technology transfer' involves the flow of expertise or technology from one place and its application elsewhere, in a two-way, ongoing activity which may cover management techniques and "best practice" as well as hardware, processes and materials."[14]

The European Biotechnology Innovation System is certainly influenced by several factors such as national al community legislation, different sectors that have a great influence for both local and supranational biotech European policy.

As it will be shown these studies portray a very different reality regarding the national innovations systems between the chosen countries. In order to better understand the differences between different member states regarding their approach towards biotechnology and their innovation processes studies from several countries

[13] Calestous Juma & Lee Yee-Cheong, 2005 "Innovation: applying knowledge in development," UN Millennium Project, Task Force on Science, Technology, and Innovation
[14] British Council 2002. Innovation and Technology Transfer http://www.britishcouncil.org/science-publications-briefing-sheets.htm

(United Kingdom, Spain, Germany and The Netherlands) were taken as a way of comparing them and gain a further view in this very specific sector.

a. United Kingdom Biotech Innovation System

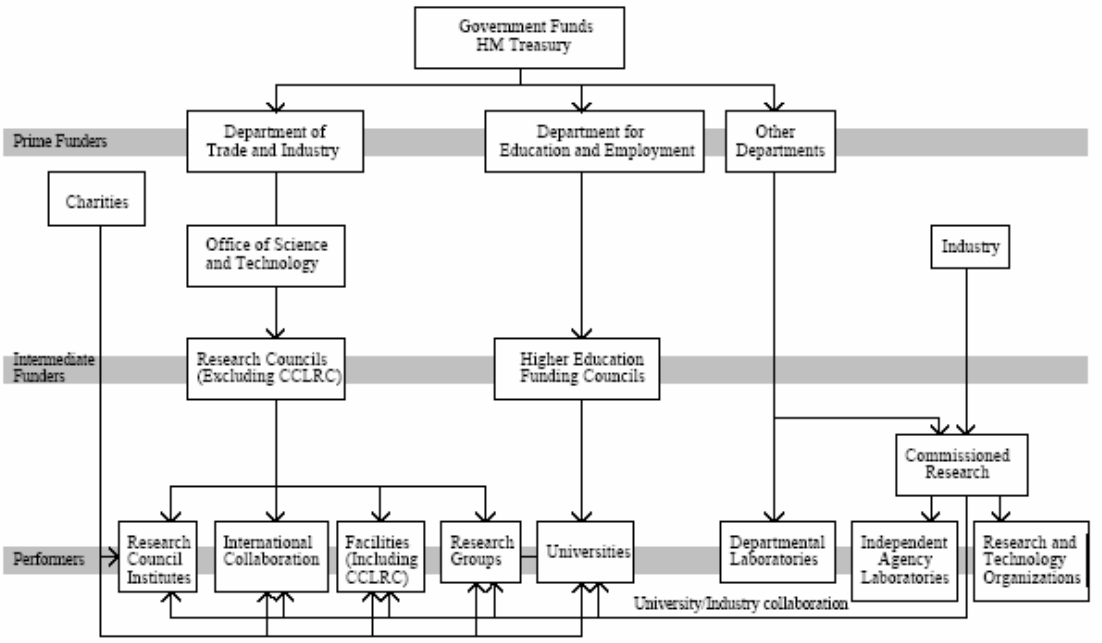
1. Biotechnology policy background

In the beginning of the 1980s the British government began having some emphasis on the biotechnology development of the country by the Spinks Report focusing in two important branches which were the developing of the scientific base and the commercial exploitation of the inventions. Later on the most targeted efforts were developed by the Biotechnology Directorate, which was established by the Science and Engineering Research Council in 1982. The Biotechnology Directorate, which was responsible for funding postgraduate students and academic research, was successful in its aims to foster a programme of strategic university research in biotechnology and to forge links between that research and industry.
Rectifying

2. Funding

Funding in the UK comes from three main sources for providing government funds to public sector research. Under the so-called "dual support system" for funding university research, the Department for Education and Employment (or relevant Departments in Scotland, Wales and Northern Ireland) pay for the basic infrastructure for carrying out research. This money is distributed by the Higher Education Funding Councils. The second source is The Office of Science and Technology, within the Department of Trade and Industry (DTI), which provides funds for research projects and this money is allocated by Research Councils to their own Institutes and to university researchers. The OST also funds the Royal Society and Royal Academy of Engineering. The third source of funds is individual government departments which commission or carry out research to support specific policy objectives. (see figure 1)

Figure 1: Research funding in the UK



[15]

To be more specific figure 2 shows in which way funding is being allocated to the biotechnology research not only from government sources but from charitable organisations.

Figure 2: Biotechnology research funding

FUNDING ORGANISATIONS	BIOTECHNOLOGY RESEARCH BUDGET (MECUS)	
Central Government and its Agencies		
Department for Trade and Industry (DTI)	9.7	
Ministry of Agriculture, Fisheries & Food (MAFF)	44.2	
Department of Health (DH)	13.8*	
Department of the Environment, Transport and the Regions (DETR)	0.8*	
The Home Office (HO)	1.9	
Scottish Office (SO)	19.6	
Welsh Office (WO)	-	
Northern Ireland Government (NI)	1.8*	
Forest Research Agency	2.2+	
Centre for Applied Microbiology & Research	16.7'	
Environment Agency	0.3	
Sub-total Central Government Ministries		111.0
Research Councils (RC)		
Biotechnology and Biological Sciences RC	286.9	
Medical RC	35.0	
Natural Environment RC	14.0*	
Engineering & Physical Sciences RC	12.0x	
Economic and Social RC	0.2	
Sub-total Research Councils		348.1
Charities/Foundations		
Wellcome Trust	67.0*	
Imperial Cancer Research Fund	13.0	
Cancer Research Campaign	6.0*	
British Heart Foundation	5.0*	
Other medical charities	28.0	
Nuffield Foundation	0.2	
Sub-total Charities/Foundations		119.2
Total		**578.3**

[16]

[15] Senker Jacqueline, Brady Max and van Zwanenberg Paddy, 2000. European Biotechnology Innovation System UK Report, SPRU, University of Sussex, Brighton. http://www.sussex.ac.uk/spru/documents/uk.pdf

[16] Senker Jacqueline, Brady Max and van Zwanenberg Paddy, 2000. European Biotechnology Innovation System UK Report, SPRU, University of Sussex, Brighton. http://www.sussex.ac.uk/spru/documents/uk.pdf

There are several programmes and institutions that support the commercialisation of biotechnology such as: (Department of Trade Industry):

- The Biotechnology Mentoring and Incubator (BMI): providing protection and guidance to new biotech firms
- Biotechnology Exploitation Platform (BEP): This programme aims to improve the administration of intellectual property issues.
- Manufacturing for Biotechnology: aims to find the production and research facilities to produce biotech products. It helps firms to find third parties (outsourcing) to streamline the production process
- Biotechnology Industry Government Regulatory Advisory Group: helps firms to have a forum for them to exchange information and to asses the regulatory framework.

3. Biotech Regulations

The United Kingdom is one of the countries (as long with China, Japan, Sweden and Belgium) with a permissive policy on embryonic stem cell research meaning that various embryonic stem cell derivation techniques could be developed including somatic cell nuclear transfer (SCNT), also called research or therapeutic cloning[17]. These countries represent a global population of approximately 2.7 billion people. (See map on Annexe b. Map of Countries with permissive policy of embryonic stem cell research)

The United Kingdoms' regulatory and advisory system in biotechnology is the one in charge of approving products and to propose the legal framework in which these processes or products must be conducted. There are several committees that tackled with different kind of deals and issues but nevertheless most of them focus with food and agriculture and medical issues that come up from the biotechnology spectrum. On the other hand there is the Health and Safety Commission and the Health and Safety Executive (HSE) which are engaged in a more bureaucratic role since they deal with issues related to the safety of workers working in the biotech industry. At the same time the HSE follows the control of the regulations about the use of GMO (genetically modified organisms).

Regulations controlling the contained used of genetically modified organisms, which have existed since 1978, are administered by the HSE. The Advisory Committee on Genetic Modification (AGCM) provides the HSE with detailed notes on good practice for complying with these regulations. ([1] Senker et al 2000)

[17] SCNT is the transfer of a cell nucleus from a somatic or body cell into an egg from which the nucleus has been removed

Most of the national regulations and legislations regarding biotechnology come from The United Kingdom Parliament (House of the Lords) from the Stem Cell Committee as in the following legislations: Medicines Act 1968 and Medicines for Human Use Regulations 1994, Health Services circular HSC1998/126 (Clinical Procedures involving Xenotransplantation[18]) under NHS Act 1977 and NHS and Community Care Act 1990.[19] One of the most comprehensive documents regarding UK Stem Cell legislation is the Stem Cell Research – Report[20] which represents the most effort to clarify all Human Stem Cell national issues.

Regarding the patenting laws it is important to mention that the UK makes available by international laws patents of intellectual property based on the European Patent Convention (EPC 1978), The EU Directive on the Legal Protection of Biotechnological Inventions (98/44/EC) and the national patent system governed by the Patents Act 1977.

4. Industry:

According to the Association of the British Pharmaceutical Industry the British pharmaceutical sector is one of the strongest sectors in the country since they have ad a surplus in its trade with the rest of the world.

The UK Biotechnology Handbook[21] indicates that there are more than 97 biotech firms in the country involved with bio-pharmaceuticals (small and medium sized) (see Figure 3). "A significant number of companies have products on the market (41%) and even more offer contract research and other service activities (57%). Some indication of the market orientation of these companies may be gained from looking at where they conduct clinical trials and secure patents. The majority of clinical trials (both those conducted alone and those with partners) take place in the UK (49%); there are equal proportions of trials conducted with US and European partners (24% of each). The highest number of patents are national, but the other patenting activities of companies demonstrate their global interests. In terms of seeking scientific knowledge, these companies rely to a great extent on collaborations with national public sector research (64%). In their technological collaborations with other companies, however, US companies predominate (42% of

[18] Process of transplanting cells, tissues or organs from one species to another like from pigs to humans.
[19] Only relevant to Human Genetics.
[20] http://www.parliament.the-stationery-office.co.uk/pa/ld200102/ldselect/ldstem/83/8301.htm
[21] Crafts-Lightly Anita & Williams Ruth, 1999. The UK Biotechnology Handbook 98/99. Westward Digital Print, Cheltenham, UK.
http://www.lub.lu.se/cgi-bin/ipchk/http://elin.lub.lu.se/link2elin?genre=article&issn=0923179x&year=1999&volume=8&issue=6&collection=ejor&pages=338-338&resid=beb46348c167517e7d329de247441565&lang=en

partnerships). The main source of both product and technology licences for these firms is the UK; but the US is the second most important source."[22]

a. Top stem cells firms in the UK

There are 11 specialised stem cells firms in the country; most of them maintain a close link with universities or other sort of research facilities. Some firms generate revenues by using their licences in stem cell processes in order to be sustainable and to finance new kind of cell therapies that normally take several years (long term). Following, a chart[23] is presented with more detailed information from these mentioned stem cell dedicated firms.

Firm	Description	Finances
Axordia	Stem cell technologies for discovery therapy. Spin-off University of Sheffield	Private firm funded by the University of Sheffield
CellCentric	Commercial exploitation of epigenetics and mechanisms that control cell functionality and fate. Spin-off university of Cambridge	Private firm funded by the Rainbow Seed fund
EpiStem	Specialises in epithelial tissue and stem cell analysis. Spin-off the Paterson Institute for Cancer Research in Manchester	Private firm and claims to produce profits.
Intercytex	Develops cell therapy products for wound care and aesthetic medicine	Private firm raised money by equity funds
Novathera	To develop the ability to deliver mature differentiated stem cells using bioactive material constructs and the manipulation of bioactive materials. Spin-off Imperial College	Private firm
Odontis	Tissue engineering of teeth based on the discovery that tooth development can be initiated by stem cells. Aims to create a biotooth. Spin-off Guy's Hospital London	Private firm funded by the Wellcome Trust University Translation Award
RegenTec	Develops cell delivery. Spin-off the University of Nottingham	Private firm funded by the University of Nottingham.

[22] Senker Jacqueline, Brady Max and van Zwanenberg Paddy, 2000. European Biotechnology Innovation System UK Report, SPRU, University of Sussex, Brighton. http://www.sussex.ac.uk/spru/documents/uk.pdf
[23] Perrin Nicola, 2005. The Global Commercialisation of UK Stem Cell Research. UK Trade and Investment. http://www.fco.gov.uk/Files/kfile/UKTIStemCellsReportAugust2005,0.pdf

Reinnervate	Research with neural stem cells. Spin-off the University of Durham.	Private firm funded by grants from the University of Durham.
Reneuron	Develop cell transplantation treatments using human somatic stem cells for neurodegenerative diseases. Spin-off Institute of Psychiatry London	Private firm and funded by Merlin Bioscience.
Renovo	Develop drugs to prevent scarring and fibrosis by promoting molecular mechanisms of tissue repair. Spin-off the University of Manchester	Private firm and funded by different organisations
StemCellSciences	Creates technologies to grow, differentiate, select and purify ESCs.	Private firm and funded by Scottish Enterprise Co-investment scheme.

Figure 3. Biopharmaceutical Companies in Great Britain[24]

TYPE	NO.			
Multinational Companies				
Domestic multinationals	3			
Subsidiaries of foreign multinationals involved in R&D	6			
Small and Medium Sized Companies	97			
1. Size distribution: 1-20	36			
21-50	26			
51-100	10			
>100	24			
Not known	1			
2. Ownership				
Independent	81			
Subsidiaries	16			
European parent	8 (1 distributor only)			
USA parent	10 (1 distributor only)			
3. Origin				
University spin-off	29			
Company spin-off	13			
Independently established	33			
Not known	22			
4. No. of SMEs reporting turnover	49 (51%)			
No. of firms with 100% biotechnology turnover	39 (40%)			
Total turnover of these firms	€163.8M			
Av. turnover of these firms	€4.2M			
No of firms with less than 100% biotechnology turnover	8*			
Total biotech. turnover of firms with other activities	€223M			
5. Activities				
No of companies selling products	40			
No. of companies providing services	55			
Contract research	36			
Contract manufacturing	16			
Other: development, custom synthesis, sequencing, testing etc.	17			
6. No. of companies conducting clinical trials	26			
No. of trials	94			
Type of trials	Phase I	Phase II	Phase III	
of which carried out alone	9	7	4	
with domestic partners	7	16	3	
with European partners	12	7	4	
with US partners	7	11	5	
with other country partners	-	-	2	
Total	35	41	18	
No. of firms reporting R&D collaborations	63			
of which with domestic PSR	209			
with European PSR	65			
with US PSR	44			
with PSR in rest of world	9			
of which with domestic companies	50			
with European companies	43			
with US companies	82			
with companies in rest of world	21			
8. Patents				
National	294			
EPO	159			
US patents	199			
Rest of World	244			
9. No. of firms receiving licensing income	28			
10. Origin of licences	National	Europe	US	Rest of World
Product licences	32	16	27	2
Technology licences	46	12	30	7
Total	**78**	**28**	**57**	9

[24] Senker Jacqueline, Brady Max and van Zwanenberg Paddy, 2000. European Biotechnology Innovation System UK Report, SPRU, University of Sussex, Brighton. http://www.sussex.ac.uk/spru/documents/uk.pdf

5. Conclusion

As seen the innovation system for biotech is quite vigorous in the UK (see Figure 4.) since the key factors industry/supply and knowledge/skills are very strong given the fact that policy makers and firms recognised on an early stage the importance of this new technology. Firms make possible the development of user-supplier relationships and also production chain networks, in which dedicated biotechnology firms can contract out the manufacture of new products or clinical trials. [25]

Its is interesting to emphasise the importance of small and medium size companies in the industry since these firms have managed to be funded and they certainly help to increase the national innovation process in the biotech sector. Some of "these firms have now grown to a considerable size and some may even achieve the goal of becoming fully-integrated" companies that in the lung run might face de acquisition by larger foreign companies.

In recent years large British multinational firms have been restructured and sold to foreign firms (partially or totally) as in the case of Astra-Zeneca, formed in 1999 by the merger of the Swedish Astra AB and the British Zeneca Group PLC[26] which on one hand as an individual firm gained financial stability and global market share and positioning but on the other hand the UKs national biotech innovation system lost autonomy since now the R&D global headquarters are located in Sweden but nevertheless Britain still maintains a solid strength on their science base.

[25] Senker Jacqueline, Brady Max and van Zwanenberg Paddy, 2000. European Biotechnology Innovation System UK Report, SPRU, University of Sussex, Brighton. http://www.sussex.ac.uk/spru/documents/uk.pdf
[26] Aztra/Seneca, 2006. http://www.astrazeneca.com/article/11148.aspx

Figure 4. Key Figures of the British Biotech Industry[27]

ELEMENT	INDICATOR
No. of dedicated biotech companies	97
No. of employees	6,500
Total biotechnology turnover 1998	400Mecus (estimated minimum)
Funders of public sector research	Medical Research Council Biotechnology and Biological Sciences Research Council Department of Health Centre for Applied Microbiology and Research Wellcome Foundation and other medical charities
No. of dedicated institutes	Medical Research Council (MRC) National Institute for Medical Research Laboratory of Molecular Biology Clinical Sciences Centre Cellular Immunology Unit Centres for Protein Engineering Unit Human Biochemical Genetics Unit Human Genetics Unit Human Genome Mapping Project Mammalian Genetics Unit Molecular Haemotology Unit Protein Function and Design Unit Virology Unit Biotechnology and Biological Sciences Research Council (BBSRC) Roslin Institute Oxford Centre for Molecular Sciences Sussex Centre for Neurosciences Centre for Applied Microbiology and Research Wellcome Trust The Sanger Centre MRC/BBSRC/Wellcome/Dept. of Health Edward Jenner Institute for Vaccine Research
No. of studentships 1994-1998 No. of PhDs awarded 1994-1998	2300 Approximately 6,000*
Regulatory/technical bodies	Advisory Committee on Genetic Testing Advisory Group on Scientific Advances in Genetics Committee on Safety of Medicines Gene Therapy Advisory Committee Human Fertilisation and Embryology Authority (HFEA) Human Genetics Advisory Commission Medical Devices Agency UK Xenotransplantation Interim Regulatory Authority (UKXIRA)
Relevant regulations**	Health Services circular HSC1998/126 (Clinical Procedures involving Xenotransplantation) Human Fertilisation and Embryology Act 1990 In Vitro Diagnostic Medical Devices Regulations, 2000 Medicines Act 1968 Medicines for Human Use Regulations 1994

*global figure excluding plant genetics, plant biochemistry and fermentation

[27] Senker Jacqueline, Brady Max and van Zwanenberg Paddy, 2000. European Biotechnology Innovation System UK Report, SPRU, University of Sussex, Brighton. http://www.sussex.ac.uk/spru/documents/uk.pdf

b. Spanish Biotech Innovation System

1. Background

Before venturing any further into the Spanish biotech sector it is important to mention the huge disparity with this Member State and the rest of the presented countries. There is a lack of information and national institutions that tackle issues relevant to our topic of interest. That is why this part is smaller than the sections from other countries and is organised in a different way.

There are three kinds of companies devoted to the biotechnology in Spain such as the *completely devoted to biotechnology* which are committed with new breakthroughs and with a clear focus for the scientific and technological innovation which most significant sectors are human and animal health, agriculture and food. The next type of biotech companies are *firms partially devoted to biotech* which main area of research focuses on the food industry but most of them do not produce but they commercialise products derived from modern techniques. Finally the third division of firms are the ones *that use this biotechnology* and that again operate mainly on the food industry. All of the above groups show homogeneous characteristics within their sectors.

Since only the first cluster of firms are devoted to real research we are only going to approach and to study this one since it is the only with relevance for this paper.

2. Finances

Between the years 1997-1998 the funds used by these kinds of firms were approximately of € 3,005,060,521 per year and the average per company was €60 millions but there are certain discrepancies so to make a more real figure we can say it is closer to €13.5 millions per company. Exports of biotech firms have been declining from € 650,601.613 in 1997 to € 528,403.83 in 1998. Nevertheless the processes and biotechnology products have a higher incidence in the export volume in the business as a total, meaning that this market is oriented to the foreign market more than to the internal one.[28]

[28] Díaz Víctor, Muñoz Emilio and Espinosa de los Monteros Juan, 2000. La empresa biotecnológica en España: un primer mapa de un sector innovador. Grupo de Ciencia, Tecnología y Sociedad Unidad de Políticas Comparadas (CSIC)

The countries to which the exports are done primarily belong to the European Union: 96% of the firms that export (27 companies) do it to the EU, and the rest to non EU countries.

Most the these firms (91%) use their own funds in order to finance the high costs that are normal in this innovation intensive industry, Public central administration (63,6%) and Autonomous Administration (/43,2%). Foreign funds have been used by 18,2% of the firms.

The financial resources are allocated in the internal expenses of R&D as the number one expense followed by the acquisition of equipment and machinery and finally external expenses of R&D.

3. Biotech Regulations

Spain is behind the UK regarding local regulations that encourage genetics and stem cell research so firms have several legislative proposals in order to increase the development of biotechnology innovation:

- Fiscal incentives policy, grants and co-financing of the biotech centres.
- Modification of the current laws, specially the Law 14/1994 and the Royal Decree 951/1997 [29] since they are anachronic and are very bureaucratic preventing the quick responsiveness of this highly responsive industry.
- Equal treatment as other National R&D programmes in order to have same amount of funding.
- Patent law reform: Reduce the cost and ease the process in order to obtain it. Suppression of ethical considerations which should be only considered when exploiting the patent.
- Modify the scientific policy in order to give more incentives to researchers and to support the link between firms and research centres.[30]

4. Industry

The Spanish industry began concentrating on this field since the 80s where the Spanish science and technology systems were revived and it can be seen in the firms modernisation and then in the product and processes incorporation to the national innovation system. This way during 1980–1984 biotechnology firms began working (8%) then increasing to 22% between 1985-1989 and then growing to an outstanding 41% in the early nineties (period of the fastest growing rate in the sector).

[29] Real Decreto 951/1997, de 20 de junio http://www.juridicas.com/base_datos/Derogadas/r0-rd951-1997.html
[30] Díaz Víctor, Muñoz Emilio and Espinosa de los Monteros Juan, 2000. La empresa biotecnológica en España: un primer mapa de un sector innovador. Grupo de Ciencia, Tecnología y Sociedad Unidad de Políticas Comparadas (CSIC) http://www.iesam.csic.es/doctrab2/dt-0101.htm

Most of the firms are privately nationally owned (63 % of the companies) and 31% accounts for privately owned multinational firms which are positioned in the food and human health sector (most of them in Cataluña and Madrid). The public sector accounts for 6% of the biotech investment. For the national firms the biotech research is their principal activity and for the multinationals it is just one more activity but not the main one.[31]

The geographical distribution of these firms is like follow:[32]

Region	Number of firms
Cataluña	42
Andalucía	27
Madrid	21
Comunidad Valenciana	21
Castilla y León	8
Aragón	6
Galicia	5
Murcia	5
Navarra	5
País Vasco	5

As seen Cataluña and Madrid are the places where the biggest concentration of firms are found followed by Andalucía, Comunidad Valenciana and Galicia. According to the market segments the existing companies are divided as "Bio-processes supply firms" (33,6%), "Food" (24,7%) and "Therapeutic: human / animal health" (19,9%). Other less important sectors are compiled under "Other health care" (12,3%), "Energy and Environment" (6,2%) and "Food: animals" (1,4%) which lack of a solid industrial grid.

From these previous data it is clearly assumed that the pharmaceutical and food biotechnology sectors are the most important in Spain.

These companies totally devoted to the biotechnology have a strong commitment with the innovation activities since they are mechanisms to develop changes in the processes and products incorporating new strategies and new technology. Eighty percent of these firms have innovated processes and 71% have innovated the final product.

[31] Sociedad Española de Genética http://seg.umh.es/Revistas/revistas.asp

[32] Díaz Víctor, Muñoz Emilio and Espinosa de los Monteros Juan, 2000.
La empresa biotecnológica en España: un primer mapa de un sector innovador. Grupo de Ciencia, Tecnología y Sociedad Unidad de Políticas Comparadas (CSIC) http://www.iesam.csic.es/doctrab2/dt-0101.htm

a. Top stem cells firms in Spain

From the countries studied Spain is the one that runs behind the rest and there were not found any firm devoted entirely to the commercialisation of stem cells nor institutes that researched only in this field. The newest kind of firms that have something to do with stem cells are the ones in charge of preserving umbilical stem cells for future therapy as Smart Cells España which is a joint venture between Laboratorios CR. Echevarne and the British Smart Cells International (they are introducing this service with the name of "Smartbaby".[33]

5. Conclusion

The group of biotechnology Spanish firms could be define as an innovative sector that recognises the importance of R&D, human resources and cooperation with other similar institutions and that are focused to export their processes and products. At the same time if compared with the UK we can see a clear financial and legal disadvantage of the industry fact that certainly causes their stem cell national innovation system to be far behind from the top EU countries.

It is natural to see why export of their technology (processes and products) is the main focus of the industry since researchers don't have enough national support (legal and financial) and certainly this jeopardises their national innovation systems since they are sending away their own R&D.

c. German Biotech Innovation System

1. Background

Germany is a highly-developed and industrialised country that according to the *Bundesministerium für Bildung und Forschung* (Federal Ministry of Education and Research) 50,5% of the industrial production is accounted by intensive R&D industries fact that makes it one of the largest world economies which relies on this sector (12,2%). Germany leads ahead of Japan (11.5 %), the USA (8.5 %) and the UK (8.0 %). [34]
Also regarding the number of patents Germany has the leading position in Europe since the number of patents from France and the UK is about half of Germany

[33] Smart Cell España http://www.smartcellsespana.com/texto/qservicio.htm
[34] Wörner Stefan, Reiss Thomas, et al, 2000. European Biotechnology Innovation Systems (EBIS) Case Studies Germany. Fraunhofer Institute Systems and Innovation Research. Karlsruhe http://www.sussex.ac.uk/spru/documents/germany.pdf

The German policy system is traditionally very plural and fragmented if we refer to the national R&D system which is based on public research institutions, such as university departments and other public institutes, with a diversity of policy players. The total gross domestic expenditure on R&D amounted to 44,758 million € in 1998 thus representing 2.33 % of GDP. The German research scene is essentially characterised by three sectors: *industry, universities and non-university establishments*. Since 1994 German business are performing more than 2/3 of the R&D budget. The rest of the budget is shared among the higher education sector (18 %) and governmental and private non-profit organisations (15 %). However, industry is only financing around 61 % of the funds thus profiting from governmental financing of about 36 % of the budget which indicates an important disparity of the amount private firms give and take from the resources.[35]

2. Funding

The BMG's departmental research activities are application-oriented and intend to generate knowledge related to departmental functions using mainly the following instruments:

- pilot projects including project funding;
- departmental research by subordinate institutions and basic funding of non-university research institutions (see Figure 1)

The BMBF (Bundesministerium für Bildung und Forschung)[36] funds several programmes that cover biotechnology to some extent. Some of theses specific targeted programmes include clinical trials aiming certain diseases. The programme main objectives are to promote health and to combat disease and to improve the structures of health research.

The funds of the BMBF focus in 4 important areas: biomedical research, especially basic research and research into the causes of disease, clinical research for the improved diagnosis and control of diseases, research and development in the field of medical technology and public health research and epidemiology including research into health care systems.

[35] Wörner Stefan, Reiss Thomas, et al, 2000. European Biotechnology Innovation Systems (EBIS) Case Studies Germany. Fraunhofer Institute Systems and Innovation Research. Karlsruhe http://www.sussex.ac.uk/spru/documents/germany.pdf

[36] Federal Ministry of Education and Research

The priorities of the BMBF are all related to the bio-pharmaceuticals (biomedical research, clinical research and medical technology) and are as follow:

The funds that are provided to the **Biomedical research** are focused in the following fields:

• "*Cancer research*: It is funded by the medical departments of universities which in the clinical sector are supported by tumour centres. Important contributors in the non-university research sector are the Stiftung Deutsches Krebsforschungszentrum and the Stiftung Max Delbrück-Zentrum für Molekulare Medizin

• *Cardiovascular research*: It is funded by the higher education sector and by non-university institutions (Forschungszentrum für Umwelt und Gesundheit)

• Molecular medicine: Is funded by the BMBF having prioritising the "Gene therapy I and II"[37]

In **Clinical research** the Bundesministerium für Bildung und Forschung focuses its funds in the following categories:

• Interdisciplinary clinical research centres

• Co-ordination centres for clinical studies at universities

• Competence networks for medicine (MedNet):

• Infectious diseases: focusing in diseases related emergencies of new pathogens as well as at controlling infectious diseases like AIDS and hepatitis and in research within tropical medicine and parasitology.

In the **Medical technology** division the BMBF's funding schemes are co-ordinated under the Health Research 2000 programme which finances specific programmes on information technology, laser research, materials research, microsystems and biotechnology." [38]

Besides the above there are several other programmes being funded as The Human Genome Research (project) that comprise the following subjects:

• exploring the structure and function of the human genetic code;

• developing new possibilities of fighting severe diseases such as cancer, cardiovascular disorders and Alzheimer's disease;

[37] Bundesministeriums für Bildung und Forschung,2005. *Forschung und Innovation in Deutschland 2005* http://www.bmbf.de/pub/forschung_und_innovation_05-07.pdf

[38] Wörner Stefan, Reiss Thomas, et al, 2000. European Biotechnology Innovation Systems (EBIS) Case Studies Germany. Fraunhofer Institute Systems and Innovation Research. Karlsruhe http://www.sussex.ac.uk/spru/documents/germany.pdf

• establishing new demand-driven technology transfer models [39]

(see figure 2 for further information)

Figure 1: Non-university institution involved in stem cell research.[40]

Name	Location	Research Organisation
Infection Biology	Berlin	MPG
Medical Research	Heidelberg	MPG
Molecular Physiology	Dortmund	MPG
Molecular Genetics	Berlin	MPG
Neurological Research	Cologne	MPG
Neurophysiological Research	Leipzig	MPG
Physiological and Clinical Research	Bad Nauheim	MPG
German Cancer Research Centre (DKFZ)	Heidelberg	Helmholtz Centres
Research Centre Jülich (FZJ)	Jülich	Helmholtz Centres
Gesellschaft für biotechnologische Forschung (GBF)	Braunschweig	Helmholtz Centres
Max-Delbrück-Centre for Molecular Medicine (MDC)	Berlin-Buch	Helmholtz Centres
Neurobiology (IfN)	Magdeburg	WGL institutes
Molecular Biotechnology (IMB)	Jena	WGL institutes
Molecular Pharmacology (FMP)	Berlin-Friedrichsfelde	WGL institutes
Primate Centre (DPZ)	Göttingen	WGL institutes
Micro-organisms and Cell Culture (DSMZ)	Braunschweig	WGL institutes
Centre of Excellence for biocatalysis and biotransformation	Düsseldorf	University and Helmholtz Centres
Surface Technology and Biochemical Engineering IGB	Stuttgart	FhG
Toxicology and Aerosol Research ITA	Hanover	FhG
Biochemistry	Martinsried	MPG
Biology	Tübingen	MPG
Brain Research	Frankfurt	MPG
Cell Biology	Ladenburg	MPG
Chemistry	Mainz	MPG
Evolutionary Biology	Tübingen	MPG
Experimental Medicine	Göttingen	MPG
Friedrich-Miescher-Laboratories for biological working groups	Tübingen	MPG
Immune Biology	Freiburg	MPG

[39] Wörner Stefan, Reiss Thomas, et al, 2000. *European Biotechnology Innovation Systems (EBIS) Case Studies Germany. Fraunhofer Institute Systems and Innovation Research.* Karlsruhe http://www.sussex.ac.uk/spru/documents/germany.pdf

[40] Wörner Stefan, Reiss Thomas, et al, 2000. *European Biotechnology Innovation Systems (EBIS) Case Studies Germany. Fraunhofer Institute Systems and Innovation Research.* Karlsruhe http://www.sussex.ac.uk/spru/documents/germany.pdf

Figure 2. Allocation of some Funds by organisation[41]

Funding Organisation	Programme/ Receiving Organisation	Total Annual Budget (million €)	Annual biotech budget (million €)	Biotech budget 1994 - 1998 (million €)
BMBF	project funding within Biotechnology 2000		111.0	555.0
	basic funds MPG, DFG, FhG		227.0	1135.0
	structural funds: HGF, WGL		166.0	830.0
BMU	Eco-research plan		0.3	1.3
BML	departmental research organisations	260.0	65.0	325.0
	Renewable Resources	27.7	3.8	19.0
BMWi	AiF-Research	89.0	31.2	156.0
Total			604.3	3021.3

3. Biotech Regulations

Before going any further with the national biotechnology regulations it is important to emphasize that Germany is categorised as having a restrictive policy or no established policy regarding stem cell research. "Restrictive policies range from outright prohibition of human embryo research to permitting research on imported embryonic stem cell lines only to permitting research on a limited number of previously established stem cell lines. Countries with a restrictive policy include (among the most restrictive) Austria, Ireland, Norway, Poland, (among the less restrictive) Germany, Italy, and the United States."[42]

The ministry which has the main responsibility for research policy, the setting up of specialised priorities, budgets, and long-term programmes on an aggregate level is the BMBF but also different organisations as the Projektträger[43] are involved in the administration of most of the countries R&D in tasks that go al the way from decision making process, funding consultancy, project assessment and diffusion, publishing and evaluating research programmes. (Wörner et al 2000)

It is important to emphasize that given the fact that Germany has a restrictive policy for stem cell research there is almost no legislation that tackles with this issue.

[41] Wörner Stefan, Reiss Thomas, et al, 2000. *European Biotechnology Innovation Systems (EBIS) Case Studies Germany. Fraunhofer Institute Systems and Innovation Research.* Karlsruhe http://www.sussex.ac.uk/spru/documents/germany.pdf

[42] Hoffman William, 2006. *Countries with a permissive or flexible policy on embryonic stem cell research* he University of Minnesota Medical School http://www.mbbnet.umn.edu/scmap.html

[43] project executing organisation

4. Industry

The industry turnover is 1.3 billion € and 59,0% of the firms were established independently, around one third grew out of PSR and only some 9 % were founded as a spin-off from another firm.

According to Wörner et al 2000 only 43 % of the firms are older than three years, 61 % have been set up between 1994 and 1998. Most of the firms (51 %) achieve 100 % of their total annual sales in biotechnology. A relatively large number of companies (23 %) make less than 20 % of their annual turnover in biotechnology. Regarding the main product market for 41 % of the firms is Germany, followed by countries in the European Union (33 %) and the USA (22 %). This division broadly also applies for services offered in biotechnology. Sixty two percent of the firms offer services related to biotechnology, 42 % are contract research organisations Almost half of the firms offer their services mainly in Germany and Europe emerged to be the main service market to 31 % of the companies and 20 % mainly focus on the US as a market place for their services. Only 12 % of the firms reported of licensing income.

Industry overview chart [44]

Number of companies	242
Number of employees	9,450
Total turnover	1,887 million €
Total biotech turnover	1,281 million €
Agencies funding research	BMBF, BMG, DFG, AiF, *Länder* ministries, *Stifterverband der Deutschen Wissenschaft*
Number of dedicated biotech institutes	28
Regulatory authorities	*Bundesinstitut für Arzneimittel und Medizinprodukte* (BfArM, Federal Institute for Drugs and Medical Devices, Bonn)
Regulations	*Gesetz zur Regelung der Gentechnik* (GenTG, genetic engineering act) Law on Medical Devices (ordinance of medical devices (MPV), ordinance on distribution channels for medical devices (MPVertrV), ordinance on the mandatory prescription of medical devices (MPVerschrV), ordinance on the installation, operation and application of medical devices (MPBetreibV)) *Embryonenschutzgesetz* (EschG, law about the protection of embryos)

[44] Statistisches Bundesamt Deutschland http://www.destatis.de/

a. Top stem cells firms in the Germany

Given the restrictive policy that the country has towards stem cell research it was not possible to identify firms that had their main focus on the stem cell market, that is why only two of the most important and relevant stem cell German institutions are mentioned in the chart below.

Institution	Description	Finances
Max-Planck-Institute of Molecular Cell Biology	Merging molecular cell biology with developmental biology	95% funded by the federal government 5% from different sources.
IPK Gatersleben	Educational institute	Funded by several institutions from the German government to the EU and foundations

5. Conclusion

Germany is a clear example of what a lack of the appropriate legislation can do to a whole industry. As stated before Germany is the innovation motor in R&D processes of Europe but unfortunately the United Kingdom surpasses Germany in the biotechnology / stem cell research and industry since their national legislations encourage the innovation systems in this very particular but crucial field.

The national competitiveness of the country in the biotech sector has the financial support of many public and private institutions but nevertheless some large German biotech pharmaceuticals had decided to locate part of the R&D labs in other member states or even outside of the union due to legal reasons.

d. Dutch Biotech Innovation System

1. Background

The Netherlands is one of Europe's smaller member states with a high income having a very strong agricultural and food sector followed by the petro-chemical one, nevertheless the total public spending on R&D is rather low, compared to other Member States.

Nevertheless the biotechnology sector is one of the most important from an international perspective. In the Netherlands three multinational companies are located that are also active in biopharmacy: AKZO Nobel (a Dutch Global Fortune 500 Company based in the Netherlands)[45], DSM (a nutritional and pharma ingredients,

[45] Akzo Nobel, 2006. Our Company. http://www.akzonobel.com/com/Our+company/aboutakzonobel.htm

performance materials and industrial chemicals. company with headquartered in the Netherlands)[46] and Solvay Pharmaceuticals (Dutch based pharmaceutical and chemical firm). Then there is Pharming, firm that develops protein therapeutics for unmet medical[47] needs using pharmaceuticals in transgenic animals. The following chart[48] gives a better overview of the Dutch national biotech perspective.

Element	Indicator
Companies	• *# of companies in the pharmaceutical sector*: 115 • *Proportion involved in biotechnology*: 43% (50 identified with biotechnology activities)
For firms involved in biotechnology	• *# of companies responding to EBIS survey*: 29 (58%) • *# of companies by number of employees*: 1-20 employees: 9 firms 21-50 employees: 8 firms 51-100 employees: 3 firms 101-250 employees: 3 firms 251-500 employees: - >500 employees: 6 firms • *# of existing firms founded in 1994-1998:* 11 • *Main target markets*: World • *Main source of technology*: Europe/USA
Turnover	• *Total turnover*: Euro 673 million • *Biotechnology proportion*: Euro 291 million (43%)
Significance of multinationals	• *Domestic*: low/medium • *Foreign*: medium/high
Location of R&D partners	• *Public sector:* Netherlands • *Private sector:* Europe
Significance of business interest non-government groups	• High
Public sector research	• *Organisations funding research*: Ministry of Education, Culture and Sciences, Ministry of Economic Affairs, Ministry of Public Health, Welfare and Sports, NWO, KNAW • *# of dedicated biotechnology research schools*: 8 research schools • *# of university departments involved in biotechnology research*: 24 • *# of biotechnology researchers 1996*: 338 fte's (scientific staff dedicated research schools) • *# of biotechnology Masters and PhDs awarded 1996*: 158 PhDs (dedicated research schools)
Regulation	• *Major regulatory authorities*: Ministry of Public Health, Welfare and Sports, Ministry of Public Housing, Infrastructure and Environment, Ministry of Agriculture, Nature Management and Fisheries • *Regulations*: Drugs and Diagnostics Act, Decree on Novel Foods, EU regulation 258/97, Chemical substances act, Decree on GMOs, EU 90/219, EU 90/220, Animal experiences act, Decree on biotechnology with animals
Leading forces of the whole sector	• International competition • Public health policies • Reimbursement policy insurance companies
Leading forces for the biotechnology part of the sector	• New developments in genomic
Inhibiting forces for the biotechnology part of the sector	• -

[46] DSM, 2006. Company Profile http://www.dsm.com/en_US/html/about/company_profile_2006.htm
[47] Pharming Group N.V.,2006. http://www.pharming.com/
[48] S. Kern & C. Enzing, 2002. The Dutch Biotechnology Innovation System: An inventory and assessment of the major developments since 1994. Netherlands Organisation for Applied Scientific Research http://www.sussex.ac.uk/spru/documents/netherlandscountryreport.pdf

2. Funding

The Dutch public biotechnology funding system is quite large and diverse and focuses in many areas of medical development note exclusively focusing in genetics and stem cell research that is why we are going to focus only in the specifics that have to do with our area of study. Nevertheless the general funding system is going to be explained by a chart (figure 1).

Most public funds come from governmental ministries, the rest from industry and charities. The funds find their way through so-called intermediate organisations to the research groups in the R&D infrastructure. These organisations exist of academic research organisations, such as the universities, the KNAW (Royal Academy of Science) and NOW (Netherlands Organisation for Scientific Research) institutes and applied research institutes such as TNO (Netherlands Organisation for Applied Scientific Research), DLO (Directorate Agricultural Research) and RIVM (National Institute of Public Health and Environmental Protection).

The main funding organisations of biopharmaceutical research are the Ministry of Education, Culture and Science and the Ministry of Economic Affairs, funding through the NOW and other programmes (see figure1).

The Ministry of Education, Culture and Sciences also funds certain programmes specifically targeting medical faculties from different universities and institutes (where more than 1400 researchers and staff are funded). In the biopharmaceutical field funding is acquired by the Council of the Medicinal Sciences (Medische Wetenschappen: NWO-MW).

Figure 1[49]: Total of funding activities for public R&D activities on biotechnology

Funding organisation	Programme or related activity	Biotechnology area	Total biotechnology budget 1994-1998 (Euro x million)
Ministry of Education, Culture and Sciences / NWO	• Structure/function of Biomolecules (SLW/CW)	Biobasic techniques	1.78
	• CW/Unilever programme	Biobasic techniques	1.34
	• Humane Genome Programme	Biobasic techniques, human/veterinary biotechnology	1.8
	• ICES MIBITON	Open to all areas	8.9
	• Top Research School CBG	Biobasic techniques, human/veterinary biotechnology	2.6-9
Ministry of Education, Culture and Sciences / Ministry of Economic Affairs	• EET	Open to all areas	5-8
Ministry of Economic Affairs	• IOP	Environmental biotechnology, industrial biotechnology, biobasic techniques	7.8
	• BTS	Open to all areas	72-76.6
	• ABON	Plant biotechnology, industrial biotechnology, biobasic techniques	15.2
	• ICES NOBIS	Environmental biotechnology	18.5
	• Cluster projects	Open to all areas	9.8
	• Technological Top Institute WCFS	Industrial biotechnology for foods/paper/etc…, biobasic techniques	9.3 (1998)
Charity funds	• Queen Wilhelmina Fund/Dutch Cancer Society	Human/veterinary biotechnology, biobasic techniques	75-100
Total			*229-268*

"The average annual budget of the MW-division is ca. Euro 3.22 million. In addition to the open calls, the NWO has special programs. The Human Genome project of NWO started as a special program (Prioriteitsprogramma) focused on hereditary diseases, including the ethical and social aspects had a total budget of Euro 5.8 million; Euro 5.58 million was NWO money, the rest was co-financed by the Ministries of OC&W, of Public Health and the EU BIOMED program.

The Foundation for Life Sciences finances biopharmaceutical research in *Bio-molecular structures and processes* and *Neuronal, endocrine process regulation and developmental biology*. *The Foundation for Chemical Research in the Netherlands* supports bio-pharmaceutical research into the biochemical aspects of medicine in key topics as:

- Nucleic acids
- Molecular genetics

[49] S. Kern & C. Enzing, 2002. The Dutch Biotechnology Innovation System: An inventory and assessment of the major developments since 1994. Netherlands Organisation for Applied Scientific Research http://www.sussex.ac.uk/spru/documents/netherlandscountryreport.pdf

- Protein research

One of the most important charities that funds biopharmaceutical research is The Dutch Cancer Society with approximately € 42,8 million per annum most of which was spend by the Dutch Cancer Institute affiliated to the Anthonie van Leeuwenhoek Hospital in Amsterdam."[50]

Overall most of the biotech funding comes from private institutions or firms (the latest not reflected on any numbers or figures on this paper) since for such a small country the Netherlands has some very large biotech firms.

3. Biotech regulations

In the early 1990s, the Dutch regulations on the biotech field were one of the most advanced in the world (especially with the Dutch Decree on Novel Foods). Later on several debates were held rising questions about safety and financial issues. As a result the regulations shown on figure 2 were obtained:

Figure 2: Specific Dutch regulations and laws concerning biotechnology activities

	Law/ regulation	Responsible ministry	Aspects covered
Contained use	-General Nuisance Act -Chemical Substances Act, Decree on GMO[51]s -EU Regulation no. 90/219 on contained use	Ministry of Public Housing, Infrastructure and Environment	Contained work with GMOs, covering workplace, experiments with GMOs
Environmental release	-Chemical Substances Act, Decree on GMOs -EU Regulation 90/220 on deliberate release	Ministry of Public Housing, Infrastructure and Environment	Deliberate release of GMOs into the environment, experiences with GMOs

[50] S. Kern & C. Enzing, 2002. The Dutch Biotechnology Innovation System: An inventory and assessment of the major developments since 1994. Netherlands Organisation for Applied Scientific Research http://www.sussex.ac.uk/spru/documents/netherlandscountryreport.pdf

[51] Geneticaly Modified Organisms

Market introduction	-Commodities Act, Decree on Novel Foods -EU Regulation no. 258/97 on Novel Foods -Drugs and Diagnostics Act	Ministry of Public Health, Welfare and Sports	Consumer safety and information with respects to foods, food ingredients, beverages, drugs and diagnostics;
Biotechnology with animals	- Animal Experiences Act - Animal Health and Welfare Act - Decree on Biotechnology with Animals	Ministry of Agriculture, Nature Management and Fisheries	Genetic modification of animals and animal experiences
Working conditions	- EU Directive no. 90/679 - Decree on Biological Agents	Ministry of Social Affairs and Employment	Exposure of employees to biological agents (among these GMOs)

S. Kern & C. Enzing, 2002

Regarding the policy concerning biotechnology, the attitude of the Dutch Government, under pressure of the Parliament, always has been one of opposition to patenting plants or animals. During the many years of debate on a European level about a directive on patenting biotechnology inventions, the Netherlands have taken many efforts to make their objections known to the European Member States. Trying to avoid the patents of animals and plants in 1998 a new law was approved prohibiting the patenting of these organisms.

A major setback was the approval by the European Parliament and the European Council of Ministers of the directive on patenting biotechnology discoveries and the Netherlands was forced to alter the current legislation and allow the legal protection of biotechnology research results, being the only member state that voted against it.

The Dutch government has always been against the patent for life and constantly defying the community directives or laws that grant some sort of patent or exclusivity for life related (genetic) issues. The most interesting fact is that this view is solely shared by the government and parliament but not by the industry which is on favour of such laws or directives.

4. Industry

The Dutch pharmaceutical industry consisted of 115 companies[52]; 5 companies produce intermediates products and the rest produce actual biopharmaceutical related products fact that shows how intensive this industry is in the country. In 1998 the annual turnover of this sector was of €1,140 million, increasing in an amount of 12,4% from the previous year. The international commerce had a surplus and grew 21,8% and from this amount 90,0% was made within European countries.

In order to further have a general image of the Dutch biotechnology industry it must be divided by indicators such as size, activities, sources of technology, turnovers, markets and products, and supplies; which will be explain in the following paragraphs:

- *Size and biotechnology activities*

The biggest amount of biopharmaceutical firms in the country is made up by small companies which have less than fifty employees. One fifth of the actual firms account for large firms which also perform R&D as their core activity. Approximately a third of the firms combine R&D activities with other activities, mostly with production. Furthermore it is very interesting to learn that the size of the firm (smaller) is correlated with the amount of trade/distribution, consultancy and services, meaning that larger firms do not perform these activities.

- *Type of biotechnology firms and its technological sources*

There are three types of firms:

  - Diversified firms: one third of the total number of Dutch firms.
  - Dedicated firms: accounts for two thirds of the market.
  - Prototype firms: number too small to be significant.

During the 90s the biopharmaceutical industry grew at a very fast pace doubling the growth rate of the agro-food and equipment sectors.

Licenses are a very important and critical issue for biotechnology firms and most licenses hold by Dutch firms come from the USA (approximately two thirds) and in spite the fact that there is a large number of firms holding Dutch patents the firms that actually produce the largest source of technology are the ones owning US based patents.

Most equipment for the firms is purchased from the USA, Europe and from the Netherlands.

- *Ownership and turnover*

[52] Statistical data from late census 1998

The majority of the bio firms in the Netherlands are domestically owned (3:5 ratio), and in some cases subsidiaries also have certain amount of national ownership. From this we can conclude that the Dutch biotech industry is indeed dominated by domestic investors. (See figure 3 for further information)

Figure 3: Turnovers of Dutch, EU & USA based firms

Type of firm	Total turnover	Biotech turnover
Domestic	€ 457,00 millions	€ 193,00 millions
Independent	€ 149,00 millions	€ 126,65 millions
Subsidiaries	€ 308,00 millions	€ 67,76 millions
7 EU & USA based firms	€ 216,00	
3 EU firms		€ 7,00 millions
4 USA firms		€ 104,00 millions

S. Kern & C. Enzing, 2002

The previous chart gives a clear image of the market turnovers and special attention should be taken to the biotech turnover of the subsidiaries if compared with the independent firms since it is two times smaller in spite that their total turnover is the double of the independent ones. This can be attributed to the fact that most of the domestic subsidiaries are trade and sales firms in comparison with the independent companies (start-ups)

Products and markets:

The national income from the biotech companies rounds about the €673 million averaging twenty six million euros per firm. The biotechnology earnings from product manufacturing and provision of services is about €291 million (43% of the total proceeds).

We can appreciate from the numbers that the national (Dutch) market is not the most important market for any of the biopharmaceutical organisation since 2/3 of all biotech companies market their products abroad.[53]

a. Top stem cells firms in The Netherlands

As in the case of Germany, The Netherlands given its very restrictive policy for stem cell commercialisation lacks of firms devoted to this kind of endeavours. Nevertheless there are biotechnological firms which as in the case of the UK have been spin-off universities like the Leiden Amsterdam Centre for Drug Research and the Leiden Institute of Chemistry both from the Leiden University. There are also spin-off firms from other

[53] S. Kern & C. Enzing, 2002. The Dutch Biotechnology Innovation System: An inventory and assessment of the major developments since 1994. Netherlands Organisation for Applied Scientific Research http://www.sussex.ac.uk/spru/documents/netherlandscountryreport.pdf

Dutch universities like Maastricht, Ultecht, Groningen and Twente (which are the biggest universities in the country.

5. Conclusion:

The Dutch biotechnology system is quite interesting and peculiar since on hand has they have a very energetic industry with many firms which certainly innovate and create added value for the national biotech knowledge pool as well as international (since they trade this technology and rely on other countries as well) but on the other hand they have a very conservative national policy that is concern with the patenting of life (not only human but animal and vegetal).

The industry has managed to flourish given the commissions biotech directive that was enforced to all Member States and that there hasn't been a real commitment by Dutch law makers to stop this important industry in the country (although their very conservative thoughts and approaches). Basically companies have been able to pursue their interests in this country using the legal ambiguity of the union's legislation and national legislation.

e. Countries comparison chart[54]

The following chart represents a summary of the description of the above countries emphasizing the national regulatory environment, the source of the fund (funding system) and the main therapies which are allowed and been developed.

Germany	
Regulation framework	Human embryo stem cell activities are very restricted (almost forbidden), although the new Merkel administration seems to be more open to this than the past one.
Funding	General funding from the Federal Government allocated to biotechnology. There is no government funding for stem cell research.
Types of research	Restrictive human embryonic stem cells and adult stem cell.
Industry	Has the second largest biotech / genetics industry in Europe just surpassed by the UK. High in equipment and suppliers and biopharmaceuticals. Focuses on the national and European market.
Stem cell Companies	Research institutes (no firms) Max-

[54] Perrin Nicola, 2005. *The Global Commercialisation of UK Stem Cell Research*. UK Trade and Investment. http://www.fco.gov.uk/Files/kfile/UKTIStemCellsReportAugust2005,0.pdf

	Planck-Institute of Molecular Cell Biology & IPK Gatersleben
Netherlands	
Regulation framework	Most embryonic research is guided by the Embryos Act but the use of embryonic stem cells is restricted. This policy will be reviewed next year (2007) by the government.
Funding	Government is granted by universities and research clusters.
Main therapies allowed	Human embryonic stem cells and adult stem cell.
Industry	Is the third largest biotech / genetics industry just behind Germany, no stem cell industry. Very high on equipment and suppliers and less high in biopharmaceuticals. Primarily focused on tissue engineering. Focused on the European market.
Stem cell Companies	No firms but only genetics institutions (spin-offs from universities)
Spain	
Regulation framework	We can say that Spain has a legislation in progress since it is expected the parliament to pass a new legislation that would allow (within very specific cases) stem cell research.
Funding	With this new legislation the government is looking forward to increase funding considerably in two clusters that are expected to be in Cataluña and Valencia.
Main therapies allowed	Human embryonic stem cells and adult stem cell.
Industry	Has the weakest biotech /genetics industry from the chosen countries, no stem cell industry (but it's supposed to change given modifications to the law later on 2006). Concentrates on producing consumables and imports technology, European market focused.
Stem cell Companies	No firms but some biotech clusters
United Kingdom	
Regulation framework	Allows embryonic and adult stem cell research and its legislation is regarded as one of the more advanced in the world. (Comprehensible, accountable and precise).
Funding	The stem cell research is funded by charities, research councils and the

	government.
Main therapies allowed	Somatic cell nuclear transfer, human embryonic stem cells and adult stem cell.
Industry	It leads Europe (and the world according to some studies) given the high investment and laws. Biggest European stem cell industry (virtually the only one) . Six leading centres. Focuses on providing the national market as well as the European one.
Stem cell Companies	Axordia, CellCentric, EpiStem, Intercytex, Novathera, Odontis, RegenTec, Reinnervate, Reneuron, Renovo, StemCellSciences.

f. Conclusion

According to the Final Report *European Biotechnology Innovation Systems* Germany, The Netherlands and UK have a well-developed biotechnology equipment and supplies sector. These countries maintain numerous institutions devoted to scientific research and education. There is also considerable investment in research by various multinational chemical and pharmaceutical companies in these countries, as well as a growing population of new biotechnology firms. National research activity provides both a market for equipment and supplies and may also stimulate the development of new generations of products. The national German and UK market are growing (specially the British one) but its sustainability could be jeopardised by the lack of an adequate policy (specially the German) by other non European countries. The businesses in The Netherlands have strong links to firms in other countries which may compensate for the relatively small domestic market.

The country that has the strongest national innovation system in the stem cell industry is the UK given the fact that is the only one that has firms devoted solely to the stem cell research and commercialisation; most of these companies had been spin-offs from different universities within the country (making its national innovation processes highly integrated).

Nevertheless all of the above countries have very different national policies and attitudes towards stem cell research and with the lack of a stem cell European legislation UK is the one taking advantage by having national laws that enables them to be ahead of the research and patents, next comes The Netherlands not because of the politicians and policy makers attitude towards the issue but because of the lack of responsiveness in tackling the matter with some restrictive national law, thus firms are capable to gain in the Dutch market and finally Germany since it has a restrictive stem cell and genetics policy.

The country that is behind (from our four studied member states) is Spain since public research funding is low compared to other countries, thus hampering demand and the development of a large pool of creative scientists. In addition, it has few biotechnology firms in the equipment and supplies sector, and though Spain has R&D-performing subsidiaries of multinational pharmaceutical companies. Also there are many concerns by the industry regarding the lack of national legislation that promotes R&D in this particular field since Spain traditionally is a country with little or no industrial activity in equipment and supplies (engineering and development of instrumentation). Fortunately a new legislation is expected to be approved by the parliament that would allow stem cell research and would enable funding to be available.

5. Patents

a. Background

The first attempt to protect new products or processes was The Paris Convention[55] (1883) which is an international convention for promoting trade among the member countries, devised to facilitate protection of industrial property simultaneously in member countries without any loss in the priority date. This was the first time when issues regarding patents, utility models, industrial designs, trademarks, unfair competition, national treatment and parallel imports were addressed by the international community as a whole[56].

After the Paris Convention was signed by different countries The Patent Cooperation Treaty (PCT) (1970) came as a very important tool to patent a product or process in many countries at once. In spite the fact that the PCT does not automatically issue patents in all the world it does provides important protection and benefits for the applicant of the patents (specially from foreign countries). Basically the PARIS Convention and the PCT work together given the fact that the PCT allows applicants of a patent to apply directly into the member countries from the Paris Convention up to one year since the initially files for the patent in the own country with a reasonably fee.[57]

Later on in 1973 The European Patents Convention (EPC) was created that gave birth to the EPO (European Patent Organisation), this way a European patent is converted into a collection of enforceable and revocable patents. It is important to emphasize that currently there is not a single EU patent, still it must be done the regular way but recently many questions have been addressed to propose a single EU wide patent that would not only protect inventions across the Union but across the world in conjunction with the PCT.[58]

So far all of these agreements or treaties have been dealing with general patents until in 1977 The Budapest Treaty on the Recognition of Deposit of Microorganisms was signed and here the main feature of the Treaty is that a "*contracting State which allows or requires the deposit of microorganisms for the purposes of patent procedure must recognize, for such purposes, the deposit of a microorganism with any "international*

[55] Lidgard Hans Henrik, 2006. IPR, Biotech & Technology Transfer Legislation. Juridiska Fakulteten vid Lunds Universitet.
[56] Patents Facilitating Centre, 2006. Paris Convention. International conventions and treaties http://www.tifac.org.in/do/pfc/pub/conven/paris.htm
[57] Eisenberg Howard M., 2001. Patent Law You Can Use , Patent Cooperation Treaty (PCT). Yale University Office of Cooperative Research. Yale University, New Haven, USA. http://www.yale.edu/ocr/invent_guidelines/docs/PCT.pdf
[58] Legislative Initiatives in European Patent Law, 2006. Community Patent European Patent Office http://patlaw-reform.european-patent-office.org/community_patent/

depositary authority"[59]", without taking into consideration of the geographical position of the authority. This Treaty makes the patent system of the contracting State more attractive because it is primarily advantageous to the depositor if he is an applicant for patents in several contracting States; the deposit of a microorganism under the procedures provided for in the Treaty will save him money and increase his security. The Treaty increases the security of the depositor because it establishes a uniform system of deposit, recognition and furnishing of samples of microorganisms.[60]

Finally the most recent international conventions to tackle with human medicine and protection of inventions were in The Convention on Biological Diversity (1992) and the Convention on Human Rights and Biomedicine (1997)[61] which is only mention since they are very broad and only compliment the previous conventions that really address patents.

b. Purpose

According to Nielsen & Whittaker a general *patent law aims to promote technical innovation and the dissemination of its fruits. The inventor gets exclusive rights to control commercial exploitation of his invention for some years and in return, he discloses detailed description of his invention, making the new knowledge available to all. This disclosure enables others (researchers etc…) to build on the achieved knowledge*."[62] Also it is important to mention here the 1998 EU Directive regarding legal protection of biotechnological inventions which original purpose is to establish legal certainty in this area within the European Community and to help European biotechnological companies to become more efficient in promoting innovation and thus attracting investment.

c. Definition

The European Commission defines a patent as a protection provider to the patent holder; this protection normally is granted for 20 years, given the holder of the patent exclusivity on the commercialisation and exploitation. At the same time a patent prevents third parties from using or reproducing such invention

[59] is a scientific institution - typically a "culture collection" - which is capable of storing microorganisms
[60]Budapest Treaty on the International Recognition of the Deposit of
Microorganisms for the Purposes of Patent Procedure, 1980. World Intellectual Property Organization
http://www.wipo.int/treaties/en/registration/budapest/index.html
[61] Lidgard Hans Henrik, 2006. IPR, Biotech & Technology Transfer Legislation. Juridiska Fakulteten vid Lunds Universitet.
[62] Nielsen Linda & Whittaker Peter, 2002. *Ethical Aspects of Patenting Inventions Involving Human Stem Cells*. Pg. 6 Opinion of the European Group on Ethics in Science and New Technologies to the European Commission. Brussels.

(within very specific guidelines). n case that any given third party wants to use such patent there must be a common agreement between the holder of the patent and them (normally called a licence.)

The granting of a patent is not an authorisation for the use of the invention. As mentioned in recital 14 of the Directive[63] ...“*a patent for invention does not authorise the holder to implement that invention, but merely entitles him to prohibit third parties from exploiting it for industrial or commercial purposes*”. It is important to emphasize that a patent is not a legal title that grants its holder the exclusive right to exploit an invention nor it is a right of ownership.

[63] The European Parliament and the Council of the European Union, 2004. Directive 2004/23/EC Of The European Parliament And Of The Council on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. Official Journal of the European Union http://europa.eu.int/eur-lex/pri/en/oj/dat/2004/l_102/l_10220040407en00480058.pdf

6. Patenting Involving Human Stem Cells

a. Patents on human embryonic inventions

As mentioned previously in the field of biotechnology it is very important to distinguish between a regular discovery and invention from the rest of the other fields since even the description of the patented product or process may be difficult for reasons that had and will be discussed. That is why the Budapest Treaty was very handy since it states the necessity of a depositary authority which will define the micro-organism by the national law of the country where such depositary is.

Nonetheless it is not sufficient the term micro-organism by itself since it's a very vague term and nowadays there are different processes (PRC) and products (PRD) which have been considered for patenting such as:

- "Isolation of stem cell from embryos or tissues (PRC)
- Culturing of stem cells (PRC)
- Enrichment of stem cells in mixture of cells (PRC)
- Genetically modifying stem cells for particular applications. E.g. to avoid rejection after a transplantation (PRC)
- Inducing stem cells to differentiate in particular ways (PRC)
- Inducing adult stem cells to undergo retrodifferentiation or transdifferentiation[64] with limited differentiation capacity towards multipotency or pluripotency. (PRC)
- Create embryos by transfer of a somatic cell nucleus to an enucleated (lacking of a nucleus)[65] egg for derivation of stem cell, giving the possibility of producing autologous stem cells which are lees likely to be rejected. (PRC)
- Create non-viable embryos by parthenogenesis[66], eliminating the need to destroy potentially viable embryos for deriving stem cells. (PRC)
- Transforming somatic cells directly into stem cells, e.g. by injecting them with stem cell cytoplasm or egg cytoplasm[67]. (PRC)
- Stem cells (PRD)
- Stem cell lines (PRD)

[64] Transdifferentiation or retrodifferentiation is the induction of adult stem cells to differentiate into cells of a tissue type different from that normally associated with the particular stem cells.
[65] The American Heritage® Stedman's Medical Dictionary, 2nd Edition http://medical-dictionary.thefreedictionary.com/enucleated
[66] form of reproduction in which an unfertilized egg develops into a new individual
[67] also called ooplasmic transfer

- Differentiated stem cells (PRD)
- Genetically modified stem cells. (PRD)"[68]

As seen all these processes and products are quite complex and in some ways very similar but the scope of them might focus in very different outcomes, it's of paramount importance not to underestimate the significance of all the patentable processes since it isn't now but in some decades where the real human benefit of all these therapies will be seen and applied to the general public. So far stem cells from a human embryo have been isolated in the US, Australia, India, Singapore, Israel, Sweden and the UK and cultured only in the UK (given its legislation and technology). It is an undeniable fact that such patents have already been granted in the US (see annexe d.) and that given the lack of legislation and decisiveness of the commission the UE is running behind the US on this topic.

While the EU policymakers still debate whether patents on human embryonic stem cells should be granted or not given the fact that specially in recent years all these genetic patents have raised a lot of questioning and concerns. Given the actual legislation it is not likely to have a patent law that tackles with the stem cell issues taken from the conventional patent law. As it is unlikely that patents for genetic inventions will be carved out from patent law. That is why there are alternatives that would help stem cell patents to be feasible right now without the need to wait for a more decisive Commission of the whole change of patent law. These alternatives are explored in order to focus on solutions for the European stem cell lack of legislation for this specific kind of patents:

- Exemptions[69]: One possibility for guaranteeing the freedom to use patented technology is to exempt certain activities from infringement. An example of this is the research or experimental use exemption that qualifies scientific research for immunity from infringement which is part of patent law laid down in the Community Patent Convention (see the 89/695/EEC Luxemburg Convention), which states in its article 27 that the rights that are conferred by a patent shall not extend to section (b) "acts done for experimental purposes relating to the subject-matter of the patented invention[70]". By this way it is possible to use the current legislation on favour of the stem cell research without infringing

[68] Nielsen Linda & Whittaker Peter, 2002. Ethical Aspects of Patenting Inventions Involving Human Stem Cells. Opinion of the European Group on Ethics in Science and New Technologies to the European Commission. Brussels.
[69] Van Overwalle Geertrui et al, 2006. Models for facilitating access to patents on genetic inventions Nature reviews. Genetics Journal
http://www.lub.lu.se/cgi-bin/ipchk/http://elin.lub.lu.se/link2elin?genre=article&issn=14710056&year=2006&volume=7&issue=2&collection=ejor&pages=143-154&resid=c1c966523071882b9a0c413f4286f9be&lang=en
[70] European Council, 1989. Agreement relating to Community patents 89/695/EEC, Luxemburg
http://europa.eu.int/eur-lex/lex/LexUriServ/LexUriServ.do?uri=CELEX:41989A0695(01):EN:HTML

the law. At a national level most some member states mimic this approach taken at a community level and some don't so still it is important to check Member States legislations to see if this approach is possible.

- Licensing agreements: This is one of the most common used instruments for activities that cannot be covered by the previous research exemption. Here the licensor and licensee have considerable freedom to choose the appropriate contract modalities and clauses as long as they do not have an anti-competitive effect. Royalties and transaction costs might be reduced to a minimum by negotiating cross licences. Cross licensing might be attractive in various settings, including cases of complementary patents and blocking patents. The exchange might concern more than two patents, or in some cases even entire portfolios[71]. Unfortunately these kinds of agreements are only useful for entities with assets for them to exchange or offer in return thus being a restrictive option for firms with no or few leverage.

- Patent pools: This option might be a title bit more complex than the previous one but its fairly simple, a patent pool is just is basically and agreement between two or more firms or entities who own patents to licence their patents to one another or to license them to third parties. This licence can be provided directly by the owners of the patent or by a newly created entity devoted to managing the pool.

- Compulsory licenses: "Under this mechanism the government or a court can compel a patent holder to license his rights. The 1994 worldwide WTO (World Trade Organization) Agreement on Trade Related Aspects of Intellectual Property Rights affirms the right of member states to grant compulsory licences and implicitly confirms their current autonomy to determine the grounds on which such licences can be granted. Normally compulsory licenses are granted in cases of dependency of a downstream patent holder on an upstream patent holder, and in cases in which the invention is not (or insufficiently) exploited. Recently, it has been suggested that the compulsory licensing mechanism can be invoked to address the potential hindering effects of patents in public health care. In this regard, the European Union has a very advanced vision since they compulsory

[71] Van Overwalle Geertrui et al, 2006. Models for facilitating access to patents on genetic inventions Nature reviews. Genetics Journal

licenses have been put for work for public health benefit of developing countries and also countries as France and Belgium have implemented licences for domestic public health issues." [72]

b. Ethics and law

So far it's clear that all member states have diverse approaches towards the legal background that enables their different national innovation systems (institutions) to research and make real progress in this R&D intensive field. Nevertheless before tackling any other issue it's important to recognise the huge ethical matters that arise given the sensitiveness of the topic.

In order to approach briefly the community law and issues that tackle with stem cell ethics it's important to refer to the Opinion of the European Group on Ethics in Science and New Technologies to the European Commission in their document No 15 where four main topics are identified as follow:[73]

"Human stem cell research is an example of bioethical value conflicts. On the one hand, the prospect of new therapies, even in the far future, is attractive in offering an alternative to organ and tissue donation. On the other hand, when this research involves the use of human embryos, it raises the question of its ethical acceptability and of the limits and conditions for such research. Embryo research has been extensively debated in the context of research carried out to improve IVF as a treatment for infertility. Embryonic stem cell research raises the following specific additional ethical questions:

New type of research to be performed on human embryos. Up until now, research that involved destroying embryos, if allowed, was limited to research on reproduction, contraception or congenital diseases. With human stem cell research, a much wider scope of research is being considered.

The use of ES cells and stem cell lines for therapeutic purposes. Human embryos used for research were destroyed after the research was completed and therefore were never used for fertility treatment. What remained was additional knowledge. Human embryonic stem cell research is aimed at creating cell lines with appropriate characteristics, in terms of purity and specificity. There is thus continuity from the embryonic cells to the therapeutic material obtained by culture.

[72] Van Overwalle Geertrui et al, 2006. Models for facilitating access to patents on genetic inventions Nature reviews. Genetics Journal

[73] McNally Eryl & Cambon-Thomsen Anne, 2004. 25 Recommendations on the ethical, legal and social implications of genetic testing. European Commission. Brussels
http://europa.eu.int/comm/research/conferences/2004/genetic/pdf/recommendations_en.pdf

The creation of embryos for research purposes. This delicate issue is now raised again since there is a scientific justification of this practice, namely the possibility of producing stem cells identical to the patient's cells and thus avoiding problems of rejection in the context of the future "regenerative medicine". At the same time, creating human embryos raises new ethical concerns. The ethical acceptability of stem cell research depends not only on the objectives but also on the source of the stem cells; each source raising partly different ethical questions. Those who condemn embryo research in general will not accept this difference, but for those who accept it, this issue is of major importance.

Issues in transplantation of stem cells. Clinical research and potential future applications in this field raise the same ethical issues as those dealt with in the EGE's Opinion on Human Tissue Banking (21/07/1998), concerning the respect of the donor, who should give informed consent to this use of the donated cells, the respect of the autonomy of the patients, their right to safety and to the protection of their private life and the right to a fair and equal access to new therapies[74]; and more recently on the EGE´s Opinion on The Ethical Aspects of Human Tissue Engineered Products (29/06/2004), where there is yet no European legislation specifically and comprehensively covering the authorisation to put human tissue engineered products on the market.[75] ,,[76]

Given the paramount importance of the previous problems it is important to recognise that from a legal point of view the principles of individual autonomy, human dignity, justice and proportionality are the ones in stake and as Article 22 of the Charter on Fundamental Rights on Cultural, religious and linguistic diversity that reads:

"Conscious of its spiritual and moral heritage, the Union is founded on the indivisible, universal values of human dignity, freedom, equality and solidarity; it is based on the principles of democracy and the rule of law. It places the individual at the heart of its activities, by establishing the citizenship of the Union and by creating an area of freedom, security and justice.

The Union contributes to the preservation and to the development of these common values while respecting the diversity of the cultures and traditions of the peoples of Europe as well as the national identities of the Member States and the organisation of their public authorities at national, regional and local levels; it seeks to promote balanced and sustainable development and ensures free movement of persons, goods, services

[74] McLaren Anne, Hermerén Göran. Ethical Aspects of Human Stem Cell Research and Use 14 Nov. 2000, Opinion of the European Group on Ethics In Science and New Technologies to the European Commission

[75] Report of the European Group on Ethics on the Ethical Aspects of Human Tissue Engineered Products. 2004. http://europa.eu.int/comm/european_group_ethics/docs/humantissueprod.pdf

[76] McNally Eryl & Cambon-Thomsen Anne, 2004. 25 Recommendations on the ethical, legal and social implications of genetic testing. European Commission. Brussels http://europa.eu.int/comm/research/conferences/2004/genetic/pdf/recommendations_en.pdf

and capital, and the freedom of establishment. To this end, it is necessary to strengthen the protection of fundamental rights in the light of changes in society, social progress and scientific and technological developments by making those rights more visible in a Charter." and with Article 6 of the Amsterdam Treaty (see annexe c.) which ensures the protection of fundamental rights at UE level based on traditional international instruments stressing the respect for national identity of all Member States.

Also it is important to recognise the base of the legislation that enables the rest to lie over it in regards of the health and R&D. Article 152 of the EC Treaty on public health that states "a*) measures setting high standards of quality and safety of organs and substances of human origin, blood and blood derivatives; these measures shall not prevent any Member State from maintaining or introducing more stringent protective measures;"*[77]. The previous clearly recognises the autonomy of the MS to create their own public health legislation in order to ensure protection to their citizens. Article 163 of the EC Treaty on research and technological development *states "1. The Community shall have the objective of strengthening the scientific and technological bases of Community industry and encouraging it to become more competitive at international level, while promoting all the research activities deemed necessary by virtue of other chapters of this Treaty."*

2. For this purpose the Community shall, throughout the Community, encourage undertakings, including small and medium-sized undertakings, research centres and universities in their research and technological development activities of high quality; it shall support their efforts to cooperate with one another, aiming, notably, at enabling undertakings to exploit the internal market potential to the full, in particular through the opening-up of national public contracts, the definition of common standards and the removal of legal and fiscal obstacles to that cooperation.

3. All Community activities under this Treaty in the area of research and technological development, including demonstration projects, shall be decided on and implemented in accordance with the provisions of this title." and article 173 of the EC Treaty certainly binds the technological development to the commissions consideration since *"At the beginning of each year the Commission shall send a report to the European Parliament and to the Council. The report shall include information on research and technological development activities and the dissemination of results during the previous year, and the work programme for the current year."*

[77] Consolidated Version Of The Treaty Establishing The European Community, 2002. http://europa.eu.int/eur-lex/lex/en/treaties/dat/12002E/htm/12002E.html

c. Patenting Human Stem Cell Inventions

So far it can be perceived that both health and technology laws are separate entities with very few things in common that could not actually allow any kind of research that pushes the stem cell and genetics envelope and here it is where the directive 98/44/EC of The European Parliament And Of The Council regarding the legal protection of biotechnological inventions which states that patent protection is necessary to encourage vital investment in the biotechnology industry. The law distinguishes between discoveries (i.e. materials that already exist and add to or extend scientific knowledge) which cannot be patented and inventions defined as covering gene sequences (ie the technical process to isolate or reproduce a natural element) which are patentable. Also the directive states that DNA or the genetic code of human beings cannot be patented but industrial applications or products involving DNA can be patented if they meet the criteria for 'invention' which include novelty, innovation and industrial applicability. This means that a particular gene is not patentable but the process leading to its discovery and isolation can be.[78] And the EUROSTEM which forms part of the European Union's Fifth Framework Programme on Quality of Life and Management of Living Resources. This project was concerned with the Ethics of Human Stem Cell Research and Therapy in Europe. Its main objectives, within a context of respect for fundamental human values, have been:

- The creation of an ethical stem cell research structure in order to clarify policies, function of researchers, rights and ethical issues.
- The evaluation of the legal EU framework (research & development of laws and regulations)
- The identifications en crucial ethical concerns that could be brought up by the research in order to have an adequate approach to all involved actors such as the community, governments and industries.

Both the directive 98/44/EC and the previous EUROSTEM system provide a somehow strong link that tackles in a community level most of the concerns regarding biotech and stem cell research from a legal and ethical point of view.

On one hand the directive 98/44/EC (from now on biotech directive) obliges the Commission to report on the scope of patents on sequences of genes which have been isolated from the human body; and the patentability of human stem cells and cell lines obtained from them and on this tone the Commission will continue to monitor the economic consequences of the differing legislative environments in Member States regarding patents on gene sequences and forbids any possibility to patent totipotent stem cells (cell that has the capacity to form an entire organism; human development begins when a sperm fertilizes an egg and creates a

[78] European Public Health Alliance, 2005. Biotechnology in Europe. Brussels http://www.epha.org/a/1886

single totipotent cell[79] meaning that are capable of developing into a human being) on grounds of human dignity. This resolution certainly is quite precise and necessary given the fact that it would be extremely controversial, unethical and even immoral to patent in the future a human being.

But on the other hand it also recognises that given the great "divergence of laws and laws among Member States, the patentability of pluripotent stem cells (cells that can develop into other types of cells but not into a human being) cannot be solved and the Commission report considers that it is premature to come to a definitive conclusion on this issue" [80]. This resolution once more shows the refusal of the commission to take a clear position on the patenting of human stem cells since it leaves the door open regarding the pluripotent stem cells manipulation.

Summing up we can say that the biotech directive does not permit patents on cloning human beings, modifying the genetic identity of human beings and the use of human embryos for industrial and commercial purposes but leaves open the gap without giving any answer to the possibility of patenting specific human stem cells that later on could be converted into further developed organs.

By now the only legislation that addresses the patentability of stem cells are national Member States legislations so this is a very sensitive and sensible area since the commission has managed not to state their position saying that it is quite premature to give a conclusion on this matter and by this ignoring the potentially lucrative and large market that stem cell therapy will represent in the near future. Nevertheless the European Parliament adopted a resolution on the trade in human egg cells (P6_TA(2005)0074).[81]

This resolution in its core states that the human body shall not be a source of financial gain given the fact that media reports at the end of December 2004 uncovered the existence of a clinic in Romania specialising in the donation of egg cells to European Union nationals, particularly UK citizens, in return for financial compensation. After this was disclosed the UK HFEA (the Human Fertilisation and Embryology Authority) sent a team to Romania to inspect rumours that involved possibly unlawful payments to donors but was incapable to find any evidence that Romanian donors were being paid more than justifiable expenses, but as a result of the above the Government from Romania closed the clinic and sent this case to the Prosecutor's Office given the fact that there is a clear possibility of serious effects on women's life and health since they

[79] MedicineNet.com, 2006. Definition of Totipotent.
http://www.medterms.com/script/main/art.asp?articlekey=18261http://www.medterms.com/script/main/art.asp?articlekey=18261
[80] European Public Health Alliance, 2005. Biotechnology in Europe. Brussels http://www.epha.org/a/1886
[81]European Parliament, 2005. European Parliament resolution on the trade in human egg cells. Planned egg cell trade.
http://www.europarl.eu.int/omk/sipade3?PUBREF=-//EP//NONSGML+TA+P6-TA-2005-0074+0+DOC+PDF+V0//EN&L=EN&LEVEL=4&NAV=S&LSTDOC=Y

could become suppliers of raw material[82] and ultimately Article 12 of Directive 2004/23/EC states that *"This directive should not interfere with decisions made by Member States concerning the use or non-use of any specific type of human cells, including germ cells and embryonic stem cells. If, however, any particular use of such cells is authorised in a Member State, this directive will require the application of all provisions necessary to protect public health, given the specific risks of these cells based on the scientific knowledge and their particular nature, and guarantee respect for fundamental rights. Moreover, this directive should not interfere with provisions of Member States defining the legal term 'person' or 'individual'"*[83] making it clear that payments or compensations for cell and tissue donations in Europe is not acceptable and that cells and tissues must not in any degree be subject to trade.

In more recent events there is the case of Case of Evans V. The United Kingdom where Natallie Evans started In-Vitro Fertilisation treatment with her then partner Howard Johnston in 2001 but he withdrew consent for the embryos to be used after they split up[84]. Currently Mrs. Evans cannot produce more eggs to get pregnant and this is the only option for her to have a family of her own and having access to this frozen embryos is the only way for her to have a baby of her baby with her own DNA. In spite the sympathy of the court towards her case the right to a family life - enshrined in article eight of the European Convention of Human Rights: "*Everyone has the right to respect for his private and family life, his home and his correspondence. There shall be no interference by a public authority with the exercise of this right except such as is in accordance with the law and is necessary in a democratic society in the interests of national security, public safety or the economic well-being of the country, for the prevention of disorder or crime, for the protection of health or morals, or for the protection of the rights and freedoms of others*[85]."- could not override Mr Johnston's withdrawal of consent.

Finally the court concludes by saying that "*by applying the appropriate principles to the case the correct approach on their view would be as follows: the interests of the party who withdraws consent and wants to have the embryos destroyed should prevail (if domestic law so provides), unless the other party (a) has no other means to have a genetically-related child; and (b) has no children at all; and (c) does not intend to*

[82] European Parliament resolution on the trade in human egg cells, 2005. Planned egg cell trade. http://www.europarl.eu.int/omk/sipade3?PUBREF=-//EP//NONSGML+TA+P6-TA-2005-0074+0+DOC+PDF+V0//EN&L=EN&LEVEL=4&NAV=S&LSTDOC=Y

[83] The European Parliament and the Council of the European Union, 2004. Directive 2004/23/EC Of The European Parliament And Of The Council on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. Official Journal of the European Union http://europa.eu.int/eur-lex/pri/en/oj/dat/2004/l_102/l_10220040407en00480058.pdf

[84] BBC News , 2006. Woman loses frozen embryos fight. http://news.bbc.co.uk/2/hi/health/4779876.stm

[85] Council of Europe, 1950. The European Convention on Human Rights http://www.hri.org/docs/ECHR50.html#C.Art8

have recourse to a surrogate mother in the process of implantation. The court thinks this approach would strike a fair balance between public and private interests, as well as between conflicting individual rights themselves. This test is neutral, because it can equally apply to female and male parties". [86]

Here we have a clear example of the determination of the court to follow the resolutions and directives that prohibit trade with cells or tissues in spite the fact that it's a very politically influence resolution.

d. Legal discrepancies between laws

So far we have seen several examples of why it is important to have a common union law that address the human stem cell patents and in this final section we will further more with some recent cases of disparities between the biotech directive, patent law and local MS legislations.

The first real controversy goes back to the proposal of the Biotech Directive when The Netherlands opposed the directive and challenged it in court case C-377/98[87] saying that it was against Article 230 EC. The Netherlands was convinced that only patentable aspect should be the biotechnological process but not the products that could be derived from this process. (They are against patenting any form of vegetable, animal or human life as well as biological material).

The Court also took the view that the international obligations of the Member States do not preclude the patentability of biotechnological inventions. In the view of the Court, neither the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPs), nor the Agreement on Technical Barriers to Trade (TBT) nor the Rio Convention on Biological Diversity, prevent the States party to those international agreements from coordinating their practices in this field by means of a Community directive. Finally the directive is very precise by saying "that all processes the use of which offends against human dignity must be excluded from patentability, that is to say in particular processes for cloning human beings, processes for modifying the germ line genetic identity of human beings and uses of human embryos for industrial or commercial purposes.[88]"

[86] European Court of Human Rights, 2006. Case of Evans V. The United Kingdom
http://news.bbc.co.uk/1/shared/bsp/hi/pdfs/07_03_06_echr.pdf

[87] Judgment of the Court of 9 October 2001Kingdom of the Netherlands v European Parliament and Council of the European Union
http://www.google.co.uk/url?sa=t&ct=res&cd=1&url=http%3A%2F%2Feuropa.eu.int%2Fsmartapi%2Fcgi%2Fsga_doc%3Fsmartapi!celexplus!prod!CELEXnumdoc%26lg%3Den%26numdoc%3D61998J0377&ei=ahNaRPe0OomiiAKB1cmOBA&sig2=ykp95PR39XwHnb4lu41D9Q

[88] European Commission Press and Information Division, 2001. Press Release No 48/01, 2001.
http://europa.eu.int/cj/en/actu/communiques/cp01/aff/cp0148en.htm

As an outcome of this legal process the Netherlands was forced to accept the directive but it certainly raised new points of discrepancy or contradictions given some terms as *ordre public* or morality (which were not very clear). It is also important to mention that as supporters of the Netherlands were Italy and Norway.

After this attempt to discredit the biotech directive came a very important controversy with one of the most controversial stem cell patent which is the so-called The Edinburgh patent (No. 0695351)[89], owned by the University of Edinburgh. The patent which was granted in late 1999 concerns a method of genetically modifying animal stem cells so as to give them a survival advantage over unwanted differentiated cells. "Biotechnology researchers face the problem that stem cells may grow more slowly than other cells and thus be crowded out. The method described in the Edinburgh patent solves this problem by making it easier to culture and isolate desired stem cells."[90]

After examining the application and granting the patent the EPO failed to insist on limiting the term "animal", which can be interpreted as extending to humans. The first protests rose against this patente by February 2000 and the next month oppositions were filed mainly by Germany and The Netherlands which have strong ethical oppositions against this kind of patented invention, since it involves embryonic (human stem cells) and its modifications. Finally the patent was upheld and modified to define the term "animal" and to prevent processes for cloning human beings, the genetic identity germ line (in particular the human one), the use of human embryos for any industrial or commercial purpose, also the genetically modifications of animals or plants without having a clear and "substantial" medical benefit.[91] The University claimed that they never had the intension of cloning human beings. Here it is interesting to see how specially these two countries who have national restrictive policies regarding stem cell research immediately opposed to this patent (which is not common when a MS oppose a patent granted by the EPO) granted to the UK, a country with a very permissive R&D stem cell policy.[92]

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[89] European Patent Office, 2002. "Edinburgh" patent limited after European Patent Office opposition hearing http://www.european-patent-office.org/news/pressrel/2002_07_24_e.htm

[90] European Patent Office, 2002. Background information on the "Edinburgh" patent, Pg. 1 http://www.european-patent-office.org/news/pressrel/pdf/backgr_3.pdf

[91] R.G.C. Jenkins & Co, 2006. Amendment to Exclude Embryonic Stem Cells http://www.jenkins-ip.com/pi_news/autumn2002/stem_cells.htm

[92] after Germany and the Netherlands initially apposed the patent the Italian government joined the opposition

We can also find discrepancies when The European Parliament expressed concern about the grant of European patent EP 1257168 B1[93] (see annex e.) since according to them it constitutes an infringement of the Directive that protects biotechnological inventions (98/44/EC). The MEPs (Member of the European Parliament) argues that in such patent is also included the possibility of patentability of "non- patentable human germ cells". That is why the MEP are disputing this patent by an official opposition before the EPO. Certainly the above must be taken into consideration by the EPO in the future to avoid having such problems regarding patents of stem cell related products or processes in spite the fact that this organization has been very meticulous about granting such patents in the past.. After the "Edinburgh patent" case (previously discussed), the EPO has stop granting patents for this kind of inventions. "Moreover, it has raised objections to the patentability of inventions pertaining to human embryonic stem cells in a number of applications that have been examined so far".[94] Once again we can see how two European institutions disagree having no real legal base to debate given the fact that the biotech directive doesn't tackle such inventions and the refusal of the Commission to give their opinion on the matter.

e. Towards the commercialisation of human stem cells

By now we had learned that there are basically two forms of stem cells, adult and embryonic, and even the simple research and investigation of the later ones are causing a lot of controversy not only from a legal but from ethical and moral points of view. The previous discussion about the legal discrepancies and the problems raised by patents on this field are no soon to be over but certainly they are looking forward to pave the way towards a future commercialisation of human stem cells.

Within the European Union the only country that has the most advanced, clear and precise legislation regarding stem cells is the United Kingdom, this giving it a privileged position not only within Europe but in a global scope and they are determined to take advantage and attain commercial value from this advantageous situation.

The possible commercial opportunities from the stem cell sector can be divided into groups mentioned below from short term to long term prospect:

[93] European Patent Office, 2005. Method Of Cryopreserving Selected Sperm Cells http://v3.espacenet.com/textdes?DB=EPODOC&IDX=EP1257168&F=0&QPN=EP1257168&RPN=EP1257168&DOC=cca34af1985009c5833bf8b78038dfaf56

[94] European Patent Office, 2005. The EPO follows the EU's Directive on biotechnology patents. http://www.european-patent-office.org/news/pressrel/2005_10_27_e.htm

- Research applications: differentiation of stem cell generated lines in the drug in the pharmaceutical industry to discover new drugs. (short term)
- Enabling technologies: creation of cell banks, research tools, and technology for clinical production (medium term)
- Therapeutics: one of the most promising (and controversial) aspects of stem cells which would enable the creation of new organs and tissues, the treatment of degenerative diseases (long term due to safety, clinical and regulatory issues)[95]

Currently within Europe the only country that allows embryonic stem cell research is the UK[96] thanks to The Human Fertilisation and Embryonic Act that establishes that embryonic stem cell research can be executed for research in infertility cases, gene abnormality, and for the development of treatments for serious genetic diseases. [97] It is important to mention that given the freedom of this Act the UK parliament was forced to create the Human Reproductive Cloning Bill that specifically among other things prohibits the implantation in a woman a human embryo that was created by other means other than fertilisation.[98]

The European Community is quite behind from taking action and tackling by harmonising Community Law giving guidelines towards the future of the commercialisation of European stem cell inventions. This is more than evident since the Commission hasn't been able to take a stand about the patenting of stem cells (as discussed previously) and moreover the Commission has not even approached the topic of commercialisation of human stem cells, thus allowing for member states to have unequal development opportunities.

The future commercialisation of stem cells (specifically embryonic ones) is far from becoming a reality and it certainly tackles with many different and diverse issues that most been foreseen and deal with right now and not to wait until its to late and the European stem cell national innovation systems have a clear and huge disparity (which is quite unequal by now). European law makers must make up their minds and tackle this issue given the fact that the stem cell industry has a huge growth potential and promises to change the way we humans live (specially the stem cell therapies).

[95] Perrin Nicola, 2005. *The Global Commercialisation of UK Stem Cell Research*. UK Trade and Investment. http://www.fco.gov.uk/Files/kfile/UKTIStemCellsReportAugust2005,0.pdf
[96] Ruling out Belgium since their research and financial scope is very small and relies a lot on other countries research.
[97] House of Commons, 1990. Human Fertilisation and Embryology Act. http://www.opsi.gov.uk/acts/acts1990/Ukpga_19900037_en_1.htm
[98] House of Commons, 2001. The Human Reproductive Cloning Bill. http://www.parliament.uk/commons/lib/research/rp2001/rp01-104.pdf

7. Conclusion

It is clear by now that the national innovation systems on human stem cells through all Member States are very different and variable depending on their inherent competitive advantages but also on their national legislations. There is a lack of a precise patent law that tackles specifically the patentability of human stem cells in the EU fact that puts the Union in an unfavourable position from other regions of the world.

Trying to extend the common patent law into human stem cells patents has clearly failed and has raised many legal and moral questions that had challenged certain decisions. That is why it is important to acknowledge the particularities of this kind of innovations in order to create a specific patent law system that deals with specific criteria which are inherent from such delicate processes.

The European Commission should also take a more decisive roll in order to answer "the question" regarding human stem cells patents which since 1998 has refused to do; this would create a more balanced legal setting for all MS and would increase competitiveness in the European biotechnology sector.

At the same time Member States must not only recognise the tremendous potential and importance of this industry but also create the right incentives and appropriate funding to increase their national stem cell innovation systems not only focusing on importing technology from third countries but creating them and empowering their scientists, universities and firms with the suitable linkages to promote long term sustainable growth.

There is no better way to describe what challenges and opportunities this topic brings that what Dartmouth ethics Professor Ronald Green discussed as the promise and pitfalls of stem cell research*: "There are two main ethical issues facing stem cell research around the world today. The upfront issue, of course, concerns the state and status of the human embryo and whether it's permissible to destroy human embryos in order to develop stem cell lines. Down the line, we're going to have a very serious set of issues around actually using them in human beings for transplant and therapeutic purposes. How safe are they? Will they become cancerous once they are implanted in an individual, and so on? What is the long-term effect of transplanting foreign material or even one's own embryonic type material into one's body?*

Therapeutic cloning is one of the most promising approaches in regenerative medicine. First of all because it permits us to produce stem cells that match your own body type. This is not an allotransplant of foreign material. It's your own cells brought back to their embryonic status.

Beyond that therapeutic cloning is very promising in teaching us how to reprogram cells from the start. The day will come--probably not in my lifetime, but beyond that--when we will be able to take a cell from a person's body and reprogram that cell back to its juvenile form. So literally give people wholly new blood systems. And the way to get there is through understanding how the egg reprograms the nuclear DNA, which occurs in therapeutic cloning. But then taking that learning and applying it to cell technologies generally.

I don't want to be uncharitable, but the current administration's approach to biotechnology by and large strikes me as disastrous. The government has repeatedly threatened punitive legislation to shut down this area. And most unfortunately, private venture capital that could support independent firms going into the area has dried up. The consequence is now that it's countries like Korea or China, which are actively funding this research from their governments, that are moving ahead in this area.

I think that by the end of the century medicine, as we know it, is going to be profoundly transformed. People who are in serious accidents will have new skin and bone from their own DNA available to them. Aging will not be stopped. We will still age. But the profound conditions of aging that limit people's independence and mobility will be addressed. New organs for people. I really see a vision of a medicine that provides people health from birth through good old age is what we're dealing with here."[99]

This topic is quite new and fascinating and somehow unexplored since results are going to be seen at least in a couple of decades that is why still there is time to modify and to tackle in a proactive way all issues surrounding the human stem cell research European innovation system since now the foundations are being built for what could be a very promising future for the Union, Member States, policy makers, firms and ultimately to human beings just like me or you.

[99] Green Ronald, 2005. The Ethics of Stem Cells (interview). Trustees of Dartmouth College http://www.dartmouth.edu/~news/releases/2005/11/30a.html

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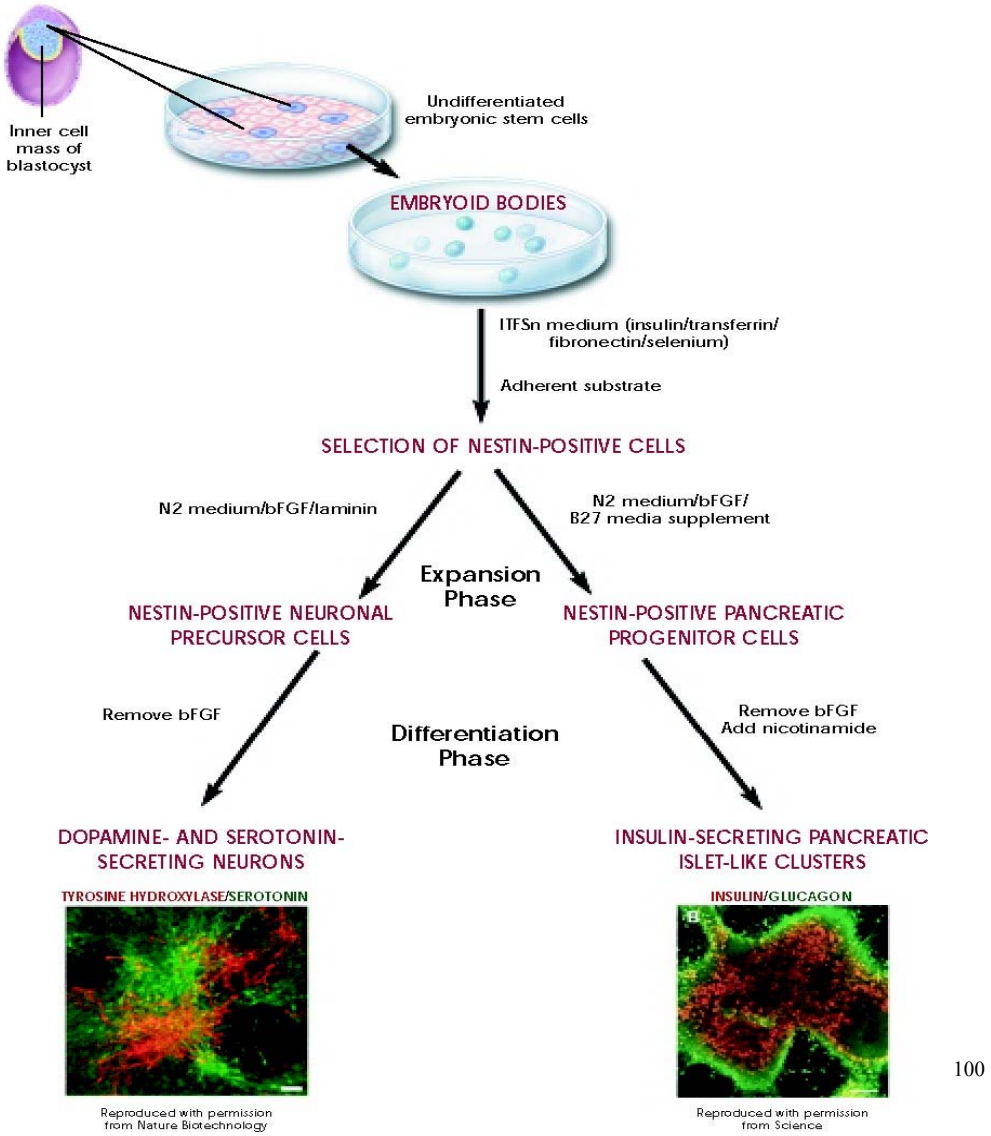
9. Annexe

a. Differentiation of cells



100

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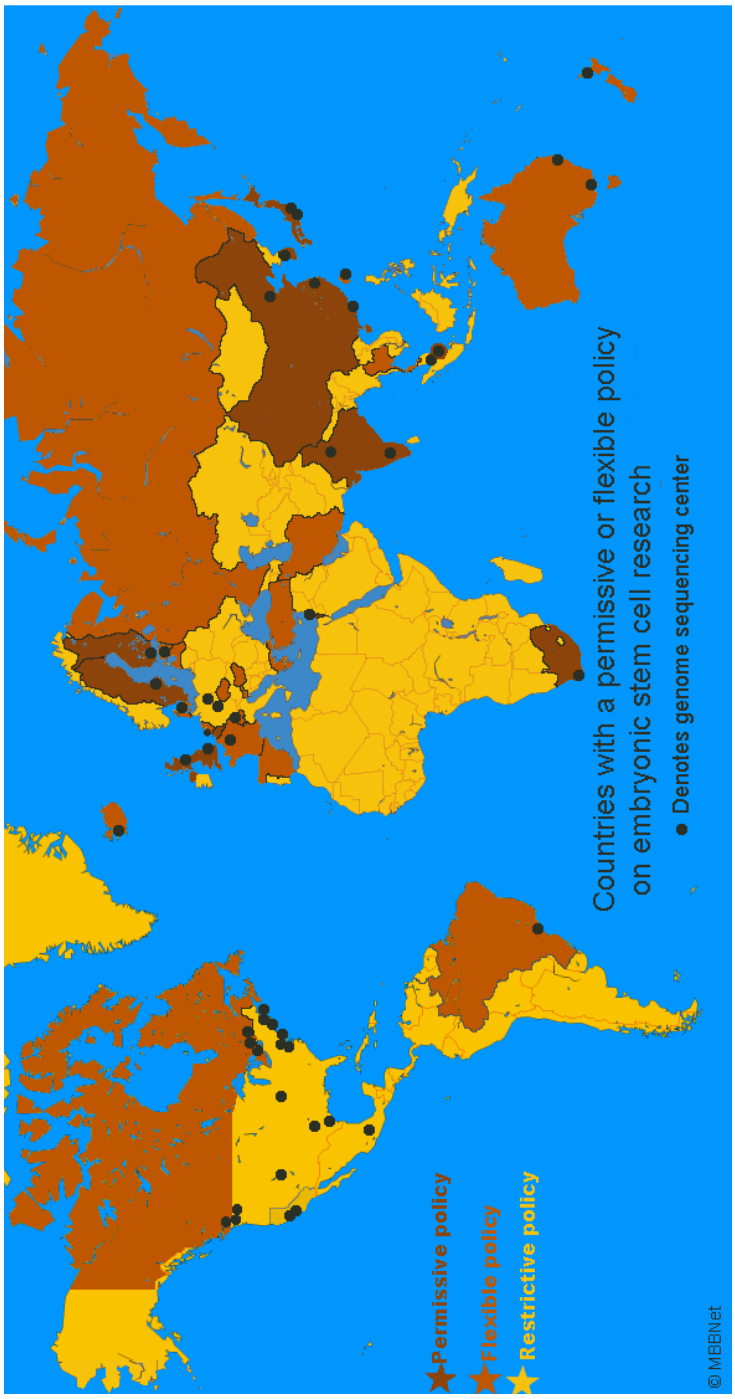
b. Map of Countries with permissive policy of embryonic stem cell research



[101]

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c. Article 6 of the Amsterdam Treaty

"1.The Union is founded on the principles of liberty, democracy, respect for human rights and fundamental freedoms, and the rule of law, principles which are common to the Member States.

2. The Union shall respect fundamental rights, as guaranteed by the European Convention for the Protection of Human Rights and Fundamental Freedoms signed in Rome on 4 November 1950 and as they result from the constitutional traditions common to the Member States, as general principles of Community law"[102]

d. Example of a US patent on human embryonic stem cells

"One example is the US patent awarded to the Wisconsin Alumni Research Foundation (WARF), for human pluripotent stem cells derived from spare embryos created for infertility treatment. This broad patent covers both James Thomson's method of isolating human embryonic stem cells (ESC) and the five undifferentiated stem cell lines derived. That patent gives WARF control over who may work with its five stem cell lines and for what purpose. WARF decided to provide access against a nominal fee to academic researchers and access against a negotiable fee to other scientists. In return for its funding of James Thomson's research, the for-profit Geron Corporation was granted a licence agreement by WARF. Geron holds exclusive rights to develop the stem cell lines isolated at the University of Wisconsin into three specific differentiated stem cell lines for commercial purposes." [103]

[102] Treaty of Amsterdam, 1997. http://www.eurotreaties.com/amsterdamtext.html
[103] Nielsen Linda & Whittaker Peter, 2002. Ethical Aspects of Patenting Inventions Involving Human Stem Cells. Opinion of the European Group on Ethics in Science and New Technologies to the European Commission. Brussels.

e. Method of Cryopreserving Selected Sperm Cells

"The present invention provides a method of cryopreserving sperm that have been selected for a specific characteristic. In a preferred embodiment, the method is employed to freeze sex-selected sperm. Although the cryopreservation method of the invention can be used to freeze sperm selected by any number of selection methods, selection using flow cytometry is preferred. The present invention also provides a frozen sperm sample that has been selected for a particular characteristic, such as sex-type. In preferred embodiments, the frozen sperm sample includes mammalian sperm, such as, for example, human, bovine, equine, porcine, ovine, elk, or bison sperm. The frozen selected sperm sample can be used in a variety of applications. In particular, the sample can be thawed and used for fertilization. Accordingly, the invention also includes a method of using the frozen selected sperm sample for artificial insemination or in vitro fertilization." [104]

[104] *European Patent Office, 2005. Method of Cryopreserving Selected Sperm Cells Abstract http://v3.espacenet.com/textdoc?DB=EPODOC&IDX=EP1257168&F=0&QPN=EP1257168&RPN=EP1257168&DOC=cca34af1985009c5833bf8b78038dfaf56*