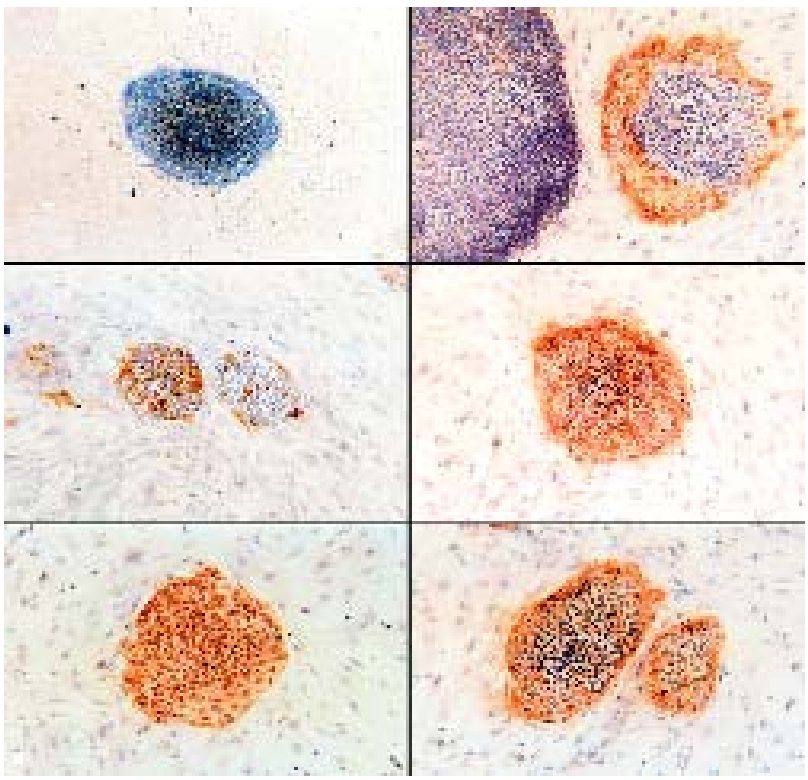
European Commission
Research Directorate-General

STEM CELL RESEARCH AT EUROPEAN LEVEL

13-14 September 2001, Brussels

MEETING REPORT



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STEM CELL RESEARCH AT THE EUROPEAN LEVEL

Foreword

This report summarises the topics, issues and policy considerations discussed at the EC Workshop on « Stem cell research at European level » held in Brussels on 13-14 September 2001. The workshop was organized by the European Commission Directorate General for Research, Directorates E and F for Life Sciences. It gathered the 12 co-ordinators from 15 transnational R&D projects specifically on stem cell research and therapy which are currently financed within the Thematic Programme « Quality of Life and Management of Living Resources ». The projects address the scientific as well as the ethical, legal and social aspects of stem cell research and therapy. Experts in law, ethics, regulatory and industrial issues were also invited. The workshop programme can be found in Annex 1. The list of participants is provided in Annex 2.

The aims and objectives of the workshop were :

- To review the scientific objectives as well as the ethical, legal and social issues linked to the research carried out within the different projects (the list of the projects is provided in Annex 3).

- To discuss the scientific opportunities and bottlenecks for development of stem cell research and therapy and how to ensure a responsible development in the field.

- To consider the future strategy for stem cell research at European level.

The report was prepared by Line Matthiessen-Guyader and Gwennaël Joliff-Botrel with the secretarial support of Stéphanie Caro and advise on english drafting from Kathryn Newell and Mark Cantley. It is based on presentations and discussions at the workshop as well as on the position papers submitted by the participants (annex 4).

The report was submitted for comments to the projects' co-ordinators and experts who participated in the workshop.

Executive summary

The European Commission has been funding stem cell research for more than a decade. It is actively following the intense debate which is taking place in many countries (not only in Europe) concerning the future of stem cell research and therapy. A debate which involves scientists, industrialists, ethicists, patient organisations, politicians and society at large. The Commission Directorate General for Research, Directorates E and F for Life Sciences is organising and coordinating pluralistic debates and scientific workshops involving all stakeholders, which will underpin its strategy for the future in this field, in particular, for the 6th Framework Programme of the European Community for Research, Technological Development and Demonstration Activities.

On 13 and 14 September 2001, the European Commission's Directorate General for Research held a meeting with 12 of the co-ordinators from the 15 transnational R&D projects specifically on stem cell research and therapy that are currently financed from the Thematic Programme « Quality of Life and Management of Living Resources»[1]. The projects address not only the scientific issues but also the ethical, legal and social aspects of stem cell research and therapy.

The research project co-ordinators, together with the legal, ethics and industry experts who joined the meeting, concluded:

- **That stem cell therapy is one of the potential new therapies** that may enable us to develop differentiated cells or tissue for transplantation into patients suffering from diseases such as diabetes, Alzheimer's, Parkinson's, stroke, chronic heart failure etc, diseases for which we today have no efficient therapy or cure.

- **Based on current knowledge, it is not possible to foresee how effective stem cell therapy will be**. Clinical applications are still at a very early stage of development and most of the very promising scientific results published and recently shown by the media, have only been obtained in small laboratory animals.

- **Society, and, in particular, the patient community, need to be made aware** of this, given the very great hopes that have been raised against the reality of actual treatment.

- **There are** grounds to be optimistic because there are already **some very successful examples** of stem cell therapies like bone marrow transplantation and skin grafting on large burns that have been in clinical practice for decades.

- **More basic research is needed** to understand how stem cells can be isolated, propagated, differentiated etc. and all possible sources of stem cells (adults, aborted foetuses, umbilical cord blood, early embryos) should be explored. Precluding exploration of any of these sources would be a short sighted decision.

- **The risk-benefit assessment, should be an essential part** of all stem cell research projects.

[1] http://www.cordis.lu/life

- **Europe needs to establish public stem cell banks** in order to ensure standardisation, quality and safety as well as easy and affordable access to the different cell lines including human embryonic stem cell lines.

- **Identification and analysis at the earliest possible stage of the ethical implications** of this new technology and encouragement for the ethical debate to become a natural part of the research and development process will be of crucial importance to ensure a responsible development and application of stem cell therapy.

- **Europe needs to develop an ethical, legal and regulatory framework for stem cell research and therapy** respecting cultural pluralism and based on identification of areas of consensus.

- **European Patenting Directive** (Directive 98/44/EEC on the Protection of Biotechnological Interventions) **concerning patenting of human stem cells require clarification.** President of the European Commission, Mr. Prodi, has therefore invited the European Group on Ethics (EGE) to prepare an opinion regarding patenting of human stem cells by the end of this year.

- **The dialogue between the public, the scientific community, clinicians, ethicists, lawyers, patients and industrialists, is essential and should be a high priority**. A public consultation should be launched in order to inform the ethical debate throughout the European Union.

This range of issues, highlights **the need for an integrated approach to the development of this technology**. Integration in this field should not only intend to reinforce co-operative links between academic research, private sector and the clinical settings, (to ensure an translational approach from bench to bedside). It should also aim at the active and early involvement of regulators, ethicists, lawyers, patients and the public at large. New or supplementary guidelines or legislation must be based on the kind of broad social agreement that can only be reached by open, two-way communication between science and society.

INTRODUCTION

Biologists value stem cells as an important tool for basic research. They are used for elucidating the mechanisms of development and cell differentiation, as vectors for the delivery of gene therapy and as a basis for development of in vitro alternatives to animal experimentation in pharmacology studies and toxicology testing. However, the current interest in stem cells arises from the prospect of using them to treat patients with degenerative diseases. Stem cells have the capacity to divide and to give rise to specialized cells which might be transplanted into tissue or organs allowing continuing regeneration in patient suffering from diseases like diabetes, Alzheimer's, Parkinson's, stroke, chronic heart failure,etc. Diseases for which we today have no efficient therapy or cure.

The European Commission has been funding stem cell research for more than a decade. The first projects concentrated on animal development and animal cell differentiation with the aim of understanding human development and to develop animal models for human diseases, in particular transgenic mouse strains. In addition some projects involved in the use of stem cells in gene therapy were and are still being funded.

The Thematic Programme "Quality of Life and Management of Living Resources" (1998-2002) currently funds 15 research projects in the area of stem cell research and therapy with a total EC contribution of 27.4 million euro. These projects range from very basic research projects aimed at understanding the basis mechanims of stem cell differentiation, propagation etc. to pre-clinical models for pathologies such as muscular dystrophy, osteodysplasias and to clinical use of hematopoietic stem cell therapy to treat patients with leukemia (see also annex 3). Several projects concentrate on neural stem cells and their potential application to treat Parkinson's disease, stroke, etc. The stem cells used in these projects are derived either from adult tissues, from umbilical cord blood or from aborted foetuses. In all cases free and informed consent has been given by the donors.

These innovative research projects cannot be implemented in a responsible way without at the same time addressing and analysing the possible ethical, legal and social implications of the research and its applications. Therefore, there is an obligation to address the ethical aspects in all research proposals submitted to the "Quality of Life Programme" and an ethical assessment takes place before the funding of a project. In addition an ethical assessment may take place during the implementation of a project. The Commission also supports transnational and multi-disciplinary research in bioethics and in particular the ethical, legal and social aspects of stem cell research and use.

MAIN SCIENTIFIC CONCLUSIONS

There is still a strong need for basic research in stem cells.

Much work still has to be done in stem cell biology. It is crucial to gain a better understanding of the underlying mechanisms regulating stem cell growth, migration, fate and differentiation. It is also of crucial importance to understand where stem cells are located and how they could be recruited to regenerate tissues and circulating cells in the adult organism.

Stem cell research should benefit from research in genomics. Studies on gene and protein profiling across the different stem cell types and stages (pre- or post-differentiation) should be essential tools that could also be helpful for better characterisation and stability control of these cells.

Research on immunology of stem cells, including stem cell grafts, are also essential for *in vivo* work and future therapies. This will allow the identification of specific new stem cell markers. Immunologically engineered human stem cells, which would not be rejected after grafting, should also be explored. This could be an alternative to the creation of embryos by somatic nuclear transfer to obtain immunologically compatible material for transplantation.

Further knowledge of all these different aspects of research is crucial to address the safety issues in clinical trials.

There is a need to continue to work on all possible sources of stem cells including early human embryonic stem cells

This was one of the strong and unanimous messages of the meeting. This field of research is still at a very early stage and it is the view of the great majority of scientists that all possible sources of stem cells should be explored (adults, aborted foetuses, umbilical cord blood, early embryos). Precluding exploration of any of these sources would be very shortsighted, and would not be scientifically justified.

Pre-clinical research has to be strongly encouraged with this new generation of stem cells (non-haematopoietic): new sets of criteria have to be defined.

Methods to properly assess the benefits and risks of this technology have to be worked out. In particular, imaging and, preferably, non-invasive technologies, are absolutely required for *in vivo* monitoring. PET and MRI should be key tools in this context.

There is also a clear need for European and international regulation and guidelines for quality/safety assessment and reference protocols for establishing cell therapy units.

The design of rational *in vitro* and *in vivo* protocols for the safety/toxicology studies, including animal models of disease, has to be worked out; GMP conditions at the different levels of the process have to be defined.

This work is complicated by the diversity of the different applications envisaged. The different therapeutic concepts of this approach compared to the traditional treatments raise

new considerations with regard to safety. For example, the need for migration of the stem cells to areas of injury or regeneration, which appears to be critical to efficacy, the fact that the engraftment may be permanent, which for brain or internal organ transplantation has necessarily specific consequences, etc.

In this pre-clinical research, which explores radically new strategies for treatments, it may be of particular relevance to work on non-human primates.

There is a need for common infrastructures and especially stem cell banks.

There is a strong request from the scientific community to have easy and affordable access to public stem cell banks that will include a collection of human embryonic stem cells. At present, only the scientific community working on haematopoietic stem cells used in clinical transplantation is benefiting from such well-organised structures. Although the situation in Europe as regards the existing different stem cell collections is rather unclear, it is very likely that they will need to be enlarged both in terms of number of cell lines and diversity in their origin, if this research is to be taken forward. However, further work is needed to ensure proper construction and use of these stem cell banks. In particular, availability of well-characterised stem cell lines is essential and standardisation/quality control methodologies have to be developed.

Scientists have also expressed concerns as regards the number of human embryonic stem cell lines actually available in the world. They stressed that it has to be made very clear to decision makers that the level of knowledge on these cells (even on their mode of cultivation) is not sufficient at present to ensure that these actual stem cells lines will be able to be maintained with their full properties indefinitely. It was also mentioned that many of the existing embryonic stem cell lines have been patented in the US. In other words, to limit stem cell research on existing human embryonic stem cell lines could hamper future development in this research.

Stem cell research also needs access to other shared facilities such as animal facilities, genomics infrastructures, statistics computing stations, cell DNA banks, various registries, GMP facilities, etc.

THE ROLE OF INDUSTRY

Regarding the exploitation of results of the stem cell research, many of the collaborations in this area with industry involve small, dedicated firms rather than large pharmaceutical companies. Small firms therefore appear to play a key role in transferring technology from this science base into industry. A number of start-ups companies have been created as spin-offs from academia in the sector. However, despite the recognised high quality of this research in Europe the "commercialisation gap" still exists and as a result the industrial position of Europe in this sector is relatively weak.

One of the current issues affecting the relationships between academia and industry is the patenting of stem cell lines. This situation has been made worse by the recent declaration of President George W. Bush of August 9, 2001 on human embryonic stem cell lines, which stressed that federal funding could only be used for research on existing cell lines. Taking into account that most of these existing embryonic stem cell lines are patented, this raises some fundamental questions.

This patent issue is not simple. On one side industry has to secure huge investments to support innovative research and development. The patent system is one method for protecting this investment and ensuring financial return. Patents also help technology transfer between academia and industry and a strong intellectual property position is often necessary for start-ups to secure venture capital investment and negotiate strategic partnerships with other industrial partners.

On the other side academia needs to have free and open access to these cell lines, as they are essential starting material for their research. Some of the scientists consider that human embryonic stem cell lines should not be patented at all. The debate on this issue is intense and includes the ethical dimension of this research. Solutions have to be found that satisfy the majority of the interested parties. But this needs deep reflection on issues and consequences and not immediate short-term decision. President of the European Commission, Mr. Prodi, has therefore invited the European Group on Ethics[2] (EGE) to prepare an opinion regarding patenting of human stem cells by the end of this year.

While many of the demonstrations of stem cell potential in animals have arisen from academia, the development of these lines into clinical products requires industrial and commercial inputs. However, it is in nobody's interest to push stem cells into clinical trials without all the issues raised here and elsewhere on safety and efficacy being properly investigated. Furthermore, stem cell therapy is an example of new innovative technologies where the translation from bench to bedside is based on a completely new scheme of development compared to the classical way of drug development. The existing regulatory schemes do not seem to apply here.

This technology is at an early stage of development and presents an opportunity to develop harmonised guidelines on quality and safety issues based on adapted criteria for assessing the efficacy of the therapy. It also presents an opportunity to involve society at large in the decision making process that will accompany the development of this technology. This approach should ensure the successful introduction of stem cell therapy.

[2] Web site : http://europa.eu.int/comm/european_group_ethics/index_en.htm#

Technical aspects of safety, quality and standardisation

The picture as regards this matter is very contrasted. On one side, there are the haematopoietic stem cells used in clinical transplantation and where considerations of all these aspects are well advanced. On the other side, there are the other stem cells. Here, the developing potential for *in vitro* expansion and even genetic modification of stem cells of both embryonic and adult origins present new considerations as regards safety, quality and standardisation aspects.

The most important points that have been raised during the meeting are:

- Embryonic stem cell stability: embryonic stem cells during passage, cryopreservation, that could influence efficacy. What are critical variables *in vitro* including purity and potency of growth factors? Reference materials for growth factors.
- Tumorigenicity : are current test systems appropriate and development of *in vitro* models ?
- Potential for activation of endogenous viruses (e.g. human endogenous retroviruses) and susceptibility to viruses potentially present in processing and cell culture media and reagents.
- Cross-reference: « Qualified » cell banks with validation data and protocols for use.
- General criteria to be confirmed for patent applications in international depositary authorities.
- Cross-reference: what are the potential safety hazards of stem cells in other transplanted tissues: detection and characterisation.
- Recommendations for minimum safety testing and monitoring of embryonic stem cells for therapeutic use.

There is no doubt that stem cell therapy in general will benefit significantly from technical standardisation to develop common good practices. This is vital for basic research to build fully characterised cell banks, prepared and validated to provide a reproducible and qualified source of cells. This will also be crucial for clinical use and considerable efforts will be needed to standardise culture conditions and reagents to assure a reproducible and safe outcome for the therapeutic use of cultures expanded *in vitro*.

Regulatory framework

The existence of a panoply of different country rules (where they exist) for all steps of development to clinical trials was recognised as a major bottleneck for the development of stem cell research and therapy. The establishment of a harmonised regulatory framework, with clear-cut rules not only for developing but also for testing and approving stem cell therapies, is regarded as an essential support to warrant a safe, efficient and responsible development of the technology.

It should be remembered that a harmonised regulatory framework already exist at EU level to deal with the development, testing and approval of biomedicine[3]. However, neither the the directives on medical devices nor on medicinal products may be applicable in a practical way. Therefore, there may be a need for the establishment of specific harmonised regulatory frameworks for certain new biomedicals such as for stem cells and their products. The Commission is in the process of examining the ground for separate regulations.

This regulation should take care of the specificities of the area. For example the highest priority should be given to strike the right balance between safety and potential quality of life of the patient. The regulatory issues should be "light" and have enough flexibility to cope with the rapid evolution of the field. The certification process needs to be rapid because the life cycle of the products is expected to be short, at least in the first years.

For a harmonious development of the market, users and producers need a stable technical frame based on standards. Those standards should for example cover the risks management or the quality system. Directorate General for Enterprise is willing to support the development of such standards.

Companies are not clear about the legislation they should apply. This is a difficult position for young companies needing transparency and legal stability before investing heavily.
The Commission is aware of this reality and cooperative activities between the different Directorates General are undertaken to put in place in Europe a frame favourable to the many start-up companies such as in the field of stem cell research and tissue engineering. It is therefore also the objectives of the European Research Area to improve the regulatory and administrative environment for research and innovation in Europe.

[3] under the responsibility of Directorate General for Enterprise and the EMEA (European Agency for the Evaluation of Medicinal Products)

ETHICAL, LEGAL AND SOCIAL IMPLICATIONS OF STEM CELL RESEARCH AND THERAPY

Ethical implications:

Human stem cell research and therapy raises ethical questions, focusing in particular on the use of embryonic stem cells. There is the need to identify and analyse the real ethical issues in stem cell research and use, which at the moment includes :

- The moral status of the embryo,
- The ethical conflict between using « spare embryos » (embryos created for infertility treatment to enhance the success rate of *in vitro* fertilization treatment (i.e. IVF), but no longer needed for this purpose) and embryos created for sole research purposes,
- Altruistic versus rewarded donation of gametes or embryos,
- Patenting of human stem cells,
- Commercialization of human stem cells.

However, other ethical issues raised by stem cells research and use also require attention. One issue that has received scarce ethical attention to date is the possibility that stem cell therapies could extend human life expectancy considerably. Issues of population policy and global justice also need to be addressed.

Bioethical research will help to guide regulators and help to inform the decision-making process by democratically elected representatives.

Legal harmonization

While respecting cultural pluralism, there is a need to identify areas of consensus in order to establish a common legal framework, recognised across Europe, which should accompany, guide and regulate these developments. Some first steps towards this harmonisation of regulatory requirements should begin at the procedural level, which includes collection, archives, distribution and processing of human stem cells. It was discussed whether the Council of Europe and its legal instruments would be the appropriated way for legal integration at European level.

Although it may be fanciful to believe that one common regulatory scheme could be implemented across the EU Member States, there is no doubt that it will be possible to draw important lessons by studying the developments in the different countries and highlighting "good" and "bad" practice with regard to regulation[4].

The distinction between spare embryos and embryos created for research should be further explored. Also the implications of the European Patenting Directive (Directive 98/44 on the Protection of Biotechnological Inventions) concerning patenting of human stem cells require clarification.

[4] In order to feed the debate, the European Commission Directorate General for Research, Directorate E, has conducted a survey on opinions from National Ethics Committes or similar bodies, public debate and national legislation in relation to human embryonic stem cell research and use. The survey is available by request (stephanie.caro@cec.eu.int)

Public consultation and information

The growing public concern about scientific progress can only be met through a rational assessment of the benefits and risks of new knowledge and new technology and through an open and structured debate on its scientific, economic, social and ethical dimensions. It is crucial that the discussions on stem cell research and use now involve scientists, ethicists, lawyers, regulators, patient organizations, the general public and policy makers. Informing the public is not enough. We need to learn to listen to the concerns expressed and to respect the diversity of ethical values and beliefs, which characterize Europe.

In a democratic society it should be considered a reasonable goal that decisions pertaining to the use of new technologies should command broad respect throughout society. It is therefore important that reflection on stem cell research and therapy becomes part of a broader public and democratic debate. The dialogue between the public and the scientific community is essential and should be a high priority. Public input is a particularly essential part of the considerations of the ethics in science. There is a need to launch a public consultation at European level in order to inform the ethical debate throughout the European Union.

THE FUTURE STRATEGY FOR STEM CELL RESEARCH AT EUROPEAN LEVEL

This meeting clearly highlights a need for activities at the European level:

- to continue to strongly support basic stem cell research using all possible sources of stem cells;
- to support research infrastructures and especially to develop stem cell line banks with European reference;
- to develop regulations for quality-safety assessment, reference practice and clinical applications of stem cell therapy (including tissue engineering);
- to assess the risk-benefit of the applications foreseen by this new technology;
- to assess the social and economic impact;
- to develop an ethical, legal and regulatory framework for stem cell research;
- to stimulate public discussion and information.

Beside all the research efforts that are strongly needed from the basic research up to the clinical research, it is the Commission view that in this field of stem cell research it is of particular importance:

- **To identify and analyse, at the earliest possible stage, the ethical implications of this new technology**. The ethical debate should become a natural part of the research and development process and it has to involve the society as much as possible. This is necessary for the responsible development of stem cell research and therapy. This can best be achieved by encouraging that ethicists, laywers and social scientists are participating in the research projects.

- **To prepare the ground for the legal and regulatory processes**, which will be essential if this new technology is to be made available to the wider public. The cell therapy is a new concept of treatment that will mean that existing regulatory frameworks may require significant adaptations. For this reason, the Commission view is that regulatory experts should become involved at the earliest possible stage of the research and development of this technology.

- That **because the industry sector operating in this field is mostly constituted of very innovative but small companies, public institutions have an important role to play** in facilitating coordination and integration of their efforts in order to build the right legal and regulatory framework to help them to compete in the future.

- **To weigh-up the risk-benefit of the technology** of each of the applications (at time of transfer into clinics).

- **To assess the socio-economic impact of the technology** (at time of transfer into clinics) taking into account constraints Europe is facing as regards public health expenses.

As highlighted in the Commission's proposal document {ref. COM(2001)279} concerning specific programmes implementing the 6th Framework Programme 2002-2006 of the European Community for research, technological development and demonstration activities, stem cell research is proposed to be among the research actions in the thematic priority 1.1.1 *"Genomics and biotechnology for health"*[5]

[5] (http://europa.eu.int/eur-lex/en/com/pdf/2001/com2001_0279en01.pdf).

New instruments are proposed by the Commission for implementing the research activities of this 6th Framework Programme, especially networks of excellence and integrated projects. These particular instruments designed for creating critical mass of research and for integrating research activities, capacities and ressources are particularly adapted to the needs of stem cell research at European level[6]. The proposal for the 6th Framework Programme is currently being discussed in the European Parliament and in the Council of Ministries.

The Commission expects that the objectives of the future projects in stem cell research will not only be directed towards exclusive scientific objectives but will also, as mentionned above, contribute to reinforce co-ordination and co-operation between the various stakeholders (basic research scientists, industrialists, standardisation bodies, clinicians, policy makers, ethicists, regulatory authorities, patients) and will include integration and involvement of society. It is the view of the Commission that this will be essential for achieving the ambitious goal of translating the stem cell research results into real benefits for society. New technologies where the development phases have to be completely re-designed, which involve also new industrialists actors like the small biotechnology companies, which are closer to the scientific world than to the industrialist one, need new concept of work and **integration**. This should help Europe to make research competitive and visible in this field as well as to increase competitiveness of its biotechnology industry in the sector. These issues are important objectives of the **European Research Area**.

[6] It is the Commission's position that the following fields of research shall not be financed under the 6th Framework Programme for Research :

- research activity aiming at human cloning for reproductive purposes,
- research activity intended to modify the genetic heritage of human beings which could make such changes heritable ;
- research activities intended to create human embryos solely for the purpose of research or for the purpose of stem cell procurement, including by means of somatic cell nuclear transfer.

Annex 1 : Agenda

STEM CELL RESEARCH AT EUROPEAN LEVEL
Expert meeting of co-ordinators of EC-funded stem cell research projects and experts in law, ethics and industrial issues

Brussels, 13-14 September 2001
Square de Meeus, 8 room 11/69

Thursday, 13 September 2001

11 :00 Welcome and introduction by L. Matthiessen and G. Joliff-Botrel

« Neural stem cells , from basic research to clinical application »

chaired by Dr. Sinden

11 :15 **Dr. Dubois-Dalcq**
« Engineering neural precursors for myelin repair »

11 :30 **Dr. Giangrande**
« Neural stem cells and stem cell-based therapies »

11 :45 **Dr. Wahlberg**
« Development of human dopaminergic neuronal cell lines for transplantation »

12 :00 **Dr. Sinden**
« European cell therapy in the nervous system »

12 :15 Discussion

13 :00 Lunch

« Stem cells, from differentiation to tissue engineering»

chaired by Dr. Cossu

14 :00 **Dr. Vainio**
« Cellular production of Wnts, secreted growth and differentiation factors and their use as co-ordinators of organ specific stem cells »

14 :15 **Dr. Cossu**
« Mesodermal stem cells : from basic biology to development of preclinical models of tissue replacement and cell therapy »

14 :30 **Dr. El Haj**
« Biomechanical interactions in tissue engineering and surgical repair »

14 :45 **Dr. Ashammakhi**
« Chondral and osseous tissue engineering »

15 :00 Discussion

15 :30 Coffee break

« Hematopoietic stem cell therapy, from bench to bedside »

chaired by Dr. Jones

15 :45 **Dr. Gluckman**
« Cord blood as an allogeneic source of stem cells for clinical use »

16 :00 **Dr. Jones**
« European Network for Foetal Transplantation »

16 :15 **Dr. Ciceri (cancelled)**
« Suicide gene therapy in stem cell transplantation »

16 :30 **Dr. Naldini (cancelled)**
« Lentiviral vectors for gene therapy of the hematopoietic system : development from bench to bedside »

16 :45 Discussion

17 :15 Break

17 :30 How to address stem cell research at the European level ?

Friday, 14 September 2001

« Regulatory issues in relation to quality/ safety assessment reference practice and clinical application »

8 :30 **Dr. Stacey** « Quality, safety and standardisation in stem cell work »

8 :45 **Mr. Bouis**, DG Enterprise «Regulatory issues : EU and US perspectives »

9 :00 Discussion

9 :30 Coffee break

« Patenting »

chaired by Dr. Quintana

9 :45 **Prof. Nielsen** « Patenting, ethics and law »

10 :00 Discussion on patenting of stem cells introduced by **Dr. Sinden and Dr. Wahlberg**

« Ethical, legal and social issues »

chaired by Dr. Quintana

11 :00 **Prof. Harris and Dr Holm** « The ethics of human stem cell research and therapy in Europe »

11 :30 **Dr. Quintana** « The opinion from the European Group on Ethics concerning the Ethical aspects of human stem cell research and use"

11 :45 **Prof. Romeo-Casabona «** Legal limitations on research and its results?»

12 :00 Discussion

13 :00 Lunch

« Public debate »

chaired by Dr. Quintana

14 :00 « How to stimulate an open two-way communication with society ? »
The role of scientists and ethicists.

Introduction by Prof. Nielsen

« Future perspectives »

14 :30 The European Research Area (ERA) and the next Framework Programme by **Mr. Bruno Hansen**, Director for Life Sciences **(replaced by G. Joliff-Botrel)**

15 :00 Discussion

15 :30 Drafting of the conclusions from the meeting and exchange of views on the conclusions.

18 :30 End of the meeting

Annex 2 : List of participants

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Annex 3 : List of funded projects

NEURAL STEM CELLS, FROM BASIC RESEARCH TO CLINICAL APPLICATION

QLG3-CT-2000-30911	Prof. Monique DUBOIS-DALCQ	Engineering neural precursors for myelin repair
QLG3-CT-2000-31224	Dr Angela GIANGRANDE	Neural stem cells and stem cell-based therapies
QLG3-CT-2000-31471	Prof. Urban LENDAHL	Neural stem cells - from basic science to CNS repair
QLK3-2001-02120	Dr Lars WAHLBERG	Development of Human Dopaminergic Neuronal Cell Lines for Transplantation
QLK3-1999-00894	Dr John SINDEN	European cell therapy in the nervous system

STEM CELLS, FROM DIFFERENTIATION TO TISSUE ENGINEERING

QLK3-2001-01275	Prof. Seppo VAINIO	Cellular Production of Wnts, Secreted Growth and Differentiation Factors and their use as Coordinators of Organ Specific Stem Cells
QLK3-1999-00020	Dr Giulio COSSU	Mesodermal stem cells: from basic biology to development of pre-clinical models of tissue replacement and cell therapy
QLK3-1999-00559	Dr Alicia EL HAJ	Biomechanical interactions in tissue engineering and surgical repair
QLK6-2000-00487	Dr Timo WARIS	Chondral and Osseous Tissue Engineering

HEMATOPOIETIC STEM CELL THERAPY, FROM BENCH TO BEDSIDE

QLK3-1999-00380	Dr Eliane GLUCKMAN	Cord blood as an allogeneic source of stem cells for clinical use
QLG1-2000-31475	Dr Rhodri JONES	European Network for Fetal Transplantation
QLK3-2001-01265	Dr Maria Chiara BONINI	Suicide Gene Therapy in Stem Cell Transplantation
QLK3-1999-00859	Dr.Luigi NALDINI	Lentiviral vectors for gene therapy of the hematopoietic system : development from bench to bedside

ETHICAL, LEGAL AND SOCIAL ISSUES

QLG6-CT-2001-00072	Prof. John HARRIS	The Ethics of Human Stem Cell Research and Therapy in Europe
QLG6-CT-1999-00517	Dr. Soren HOLM	Empirical methods in bioethics

Annex 4 : Position papers

Opinion paper on Stem Cell Research
(written at the request of the European Community Fifth Framework program)

Prof. Monique Dubois-Dalcq, MD, Pasteur Institute, Paris, France

How could a biologist not be fascinated by stem cells from which all cells of the body and organs originate ? The outstanding questions in the field are: what are the molecular signals that control stem cell growth, their turnover, life and death, their migration, fate and differentiation during development? Where do they reside and how are they recruited to regenerate tissues and circulating cells in the adult organism?

To study development of primate stem cells is of particular interest since the timing of the generation of specialized cells and tissues differs between primates and laboratory rodents, and since these differences may have resulted in changes in the physiology of the corresponding stem cells. Fortunately, comparative gene expression can be studied today more rapidly and accurately than ever before. Decades ago, stem cell multipotentiality has been observed in the hematopoietic system but now is recognized to extend to other tissues such as muscle, skin, brain, liver etc. Yet years of research efforts are still needed to precisely dissect the mechanisms involved in the generation by stem cells of the many different cell types required to assemble a living organism. Thus, stem cell research is a broad embryonic and developmental field set to discover the nature of extracellular and intracellular signals required for multipotential cells to develop into specialized and functional cells in the mature animal or man. Importantly, it is also a field of cell regeneration since stem cells can persist in several organs throughout life. Thus, the study of stem cell biology can lead to pharmacological approaches to mobilize stem cells existing in the adult organism and stimulate them to fully differentiate to replace cells that degenerate during the course of a disease.

In the case of the nervous system, stem cell biology will help us understand how the brain is assembled and how neurons and myelin-forming cells, which are essential to normal nervous system function, may be regenerated. We need to study neural stem cells from flies to man to understand how the molecular mechanisms underlying their development evolved during evolution. Concerning neuronal regeneration, transplants of nigral fetal precursors in the striatum have been beneficial to a number of patients with Parkinson Disease since over a decade. In a recent retrospective analysis, Olle Lindvall (at the World Neurology Congress in London in June 01, 2001) reviewed that, after a decade of clinical transplantation and analysis, evidence of striatum re-innervation was clearly demonstrated in two patients while PET imaging recently revealed normalized dopamine synthesis and release after such nigral transplants (see review by Bjorklund and Lindvall, *Nature Neuroscience* 3, 537-544, 2000). As one can generate today dopaminergic neurons from mouse ES cells, these advances in stem cell biology are redirecting the focus on animal experiments to assess future therapies in this devastating disease that affects mostly the aging brain. In the field of demyelinating diseases such as multiple sclerosis, which often starts in the young, a recent breakthrough has been the generation from mouse ES cells of myelin-forming cells able to myelinate axons after grafting in myelin deficient rats (Brüstle et al, *Science* 285, 754, 1999).

In human stem cell research, we should be able to use existing human embryonic stem cell lines and develop more of these as needed, using supernumerary frozen blastocysts with donor consent. Although the legislation in France has not been modified yet, the prime minister has reacted favorably last year to such proposal by a group of scientific experts.

The US president has restricted federal funding to research on ES cell lines available as of August 9, 2001, but these are unlikely to provide enough genetic diversity and potential to differentiate into all desired cell types. In addition, these cell lines often come with strong proprietary and patent restrictions as pointed out recently in the american press by James Thomson who pioneered the first human ES cell lines derived from frozen embryos in Wisconsin, USA. (Wi Cell indeed charges 5000 $ dollars for providing one cell line and has a licensing agreement with Geron which in turn has exclusive rights to generate 6 different cell types from these cells). The argument that cutting edge research and technology is mostly performed in industry has not always proven true. The recent completion of the human genome sequence has shown that publicly funded research has the advantage of freely providing access to new genetic information while each sequence obtained by the frontier technology company Celera requires a fee to access. There are also several examples of important drugs, such as Taxol, that were initially developed by publicly funded research in the US (supported by the National Insitutes of Health or NIH).

Banks of well characterized human ES cells should be made available at the European level as proposed by McLaren and Hermeren in their November 2000 EC report on « Ethical aspects of human stem cell research and use ». We agree with these authors that the results of human stem cell research should be widely disseminated and not hidden for commercial reasons. Thus, human ES cell research should be funded by tax payer money. This should permit to strictly regulate the ethical aspects of such research with the appropriate European and/or national committees, in order to avoid risks of commercial exploitation of women as a source of oocytes and human embryonic material (ibidem p16, 17). Individual consent in the absence of commercial pressure is mandatory to obtain frozen blastocysts to derive appropriate cell lines that could generate differentiated cells and tissues. The private sector should not control or own human ES cells, ie newly developed human cell lines should not be patented. In the field of therapeutic applications, collaborative research between government, academy and industry could be performed to develop frontiers technologies and/or suited animal models. In particular, pharmacological approaches could be designed to recruit endogenous stem cells to the site of disease or injury .

In most transplantation approaches to alleviate diseases, it is often important to perform autologous grafting to avoid rejection. One way to approach this is to obtain autologous stem cells from blastocyts generated by injection of adult cell nuclei into donor oocytes. This approach has recently been successful in mice where a variety of cell types were obtained including dopaminergic neurons (Wakayama et al, *Science 292*, 740, 2001). In parallel, one should attempt to engineer human ES cells that would not be rejected after grafting. Both lines of research should be pursued as it is hard to tell which one might be more successful. Whenever appropriate non human primate models of human diseases exist, stem cell therapeutical approaches should be first studied in the primate before a clinical trial is considered. Thus, non human primate ES cell lines should also be derived.
To conclude, stem cell research, already well funded by the EC, should be broadly supported in the future and facilitated by an international network of human ES cell lines banks. This would be highly beneficial to the patients in the EC when the time will come for clinical trials. Most importantly, we should adopt between the different EC countries a common policy and sets of criteria for quality/safety assessment and evaluation of the efficiency of a particular clinical trial so that clear conclusions can be drawn from those studies. In addition, we need to improve our ways of communicating with the public to inform them about what scientists know, think and do in this area of research in order to eliminate fear and misunderstanding. It is paramount to stress that human pre-implantation embryos (fertilized eggs to blastocyts) are far from being « embryos » in the common language sense of being tiny humans with heads, feet, hands and beating hearts. For this

education of the public, a European website and television network of broadcasts on the nature of stem cell biology and its potential for therapy of major human diseases should be rapidly established. The public should also be informed on how taxpayer money is used to promote the field of stem cell research through a dialogue between government, academic and industry experts (see comment in *Science 293, 1575, 2001*). In this endeavour, we should also reach out to areas of the world with lower economic development.

ECTINS – Neural Stem Cells as a Viable Therapeutic for the Damaged Brain – Background Discussion

Dr. John Sinden, ReNeuron, United Kingdom

1. What are Neural Stem Cells?

Stem cells are found in the developing brain migrating from ventricular and/or subventricular zones to form all neural structures. Neural stem cells have the same definitional features as all other stem cells and are delimited by their ability (1) to self-replicate and (2) to differentiate into all cell types that form the CNS – neurons, glia and oligodendrocytes. Given the right environmental signals, neural stem cells may also give rise to cells that normally originate in the neural crest such as smooth muscle and Schwann cells, and have been shown to repopulate bone marrow and muscle and give rise to blood cells and muscle cells respectively. This gives rise to the exciting possibility that stem cells may be truly generic and, when given appropriate signals, able to give rise to any kind of mature cell. Recent evidence suggests that the side population phenotype expressing the ABC transporter Bcrp1/ABCG2 marker may represent a common marker of stem cells found in all organ systems. Progression to differentiation may not even be one-way since recent research suggests that some mature cells and committed precursors may revert to an earlier stem cell form. In the adult brain stem cells are maintained as normally quiescent cells near the ependemi. They are upregulated in response to injury and retain their capacity to migrate. Thus there may be an endogenous repair mechanism in the CNS waiting to be kicked into action. However, since we do not know how to stimulate adult cells into self-repair, efforts have focussed on grafting of exogenous stem cells from many sources for repair of brain and body.

2. Why Transplant Stem Cells

A. Problems associated with primary tissue grafts

To date, the major source of tissue for CNS grafting has been cadaveric fetal material, and the main strategy has been to provide transmitter-releasing cells to alleviate conditions associated with loss of a specific neural system, such as dopamine in Parkinson's disease (PD). Although the potential of structural repair has been investigated in animal studies, this has rarely reached clinical investigation. The protracted experimental use of fetal tissue grafts (only about 300 patients worldwide have been grafted over the past 10 years; there are 4 million PD patients worldwide) attests to the severity of the practical and ethical problems that beset this approach. These problems include:

- Ethical Issues: termination of pregnancy; appropriate counselling of donors; informed consent combined with donor anonymity; screening donors and issues surrounding testing for HIV; concerns of healthcare staff; need for balanced representation of views within local ethical committees whose approval is mandatory; impact of political pressure groups; use of placebo surgery procedures.
- Logistical problems: typically tissue from several fetuses is combined – up to 8 fetuses have been used in PD patients. This creates difficulties in timing terminations to obtain tissues of similar gestational age. If fresh tissue is stored then viability is reduced, and if cells are cultured the nature of the grafted population may change.

- Efficacy: Results from the open label Swedish series have been promising. However, the first double-blind placebo controlled trial (Denver/New York: Freed et al., NEJM 344: 710-719, 2001) revealed improvements only in younger patients and worsening dyskinesias in 5/33 patients.
- Immunosuppression, possible liver toxicity with standard drugs
- Safety issues: only limited screening of tissue is possible; lack of quality assurance.
- Problematic graft characteristics – variable graft survival, lack of integration into host architecture, possible host cytotoxicity

3. Do Stem Cells Overcome the Problems Posed by Fetal Grafts?

- Ethical issues: Stem cells derived from primary fetal tissue reduce but do not eliminate concerns about destruction of potential human life, since expansion of cells in culture may vastly reduce the requirement for fresh tissue. There are considerable national differences in the public perception of stem cells derived from human embryos and/or fetuses ranging from the pragmatic (eg UK), through to outright prohibition (eg Germany), although the public debate is now very open in all industrialised nations.
- Logistical problems: Ready expansion of stem cells makes possible the development of transplant therapy for a much wider range of patients with intractable neurological disease than heretofore. If human trials using stem cell transplants are successful, then the transplant infrastructure across European health services will need considerable expansion.
- Efficacy: Animal studies have suggested that stem cell grafts may be as effective as tissue grafts in head-to-head comparisons, as a consequence of the relatively more prominent migratory and integrative capacity of stem cells. However, it is too early to comment on the clinical efficacy of stem cell grafts other than the now routine success of bone marrow and blood-borne stem cell grafts.
- Immunosuppression: Stem cells appear to have reduced expression of MHC Class II molecules compared to differentiated cells, but it is not known how far immunosuppressive treatments will be required
- Safety issues: Undifferentiated, mitotic and migratory stem cells raise a number of safety issues, particularly regarding overgrowth or tumour formation. However, if stem cell lines are stably cloned, then appropriated *in vitro* and *in vivo* assays can reduce or negate these risks. Well-characterised clonal cell lines are therefore more likely to receive safety approval than heterogeneous primary cells or mixed populations.
- Graft characteristics: The damage-dependent migratory and selective engraftment characteristics of stem cells make them both more efficacious and less likely to damage the host brain than standard tissue transplants which lodge and develop at the point of implant. The flexibility of stem cells as a therapeutic is also indicated by the possibility of using them to transport genes, enzymes, trophic factors, tumour treatments and other therapeutic agents to sites of disease.

4. Stem Cells Have Multiple Uses

Stem cells offer multiple opportunities for a range of products with scientific, clinical and commercial high value.

Stem cells can be used for the investigation of:

- Brain development, growth factors that influence differentiation along divergent developmental routes.
- Signalling systems that govern cell migration

- Graft mechanisms in different models of brain disease/damage, e.g. cell replacement, cell stabilization, trophic support preventing or reversing cell death, etc.
- Patterns of gene/protein expression that characterize cells lines that differ in their capacity to repair the damaged CNS.
- Factors that might enhance the proliferation, migration and differentiation of endogenous stem cells in the damaged brain
- Region specific stem cell lines as tools for drug discovery: live cell screening, pharmacogenomics, pharmacoproteomics, toxicology, etc.
- Novel target discovery from low abundance genes found in stem cell lines.

5. Are Stem Cells Too Good to be True?

The flexibility and potentially wide applications of stem cell grafts should not blind us to the unknown potential uncertainties about their potential as therapeutics.
These include:

- Cell stability: Extensive growth of stem cells, like all somatic cells, poses risks of karyotype instability. Defining acceptable stability criteria needs to be established
- cGMP cell production: Few stem cell lines have been developed under 'clinical grade' conditions. For example, none of the 60 embryonic stem cell lines identified by the US government have been developed under quality assurance and control of raw materials in production. Therefore, they could not transfer from the lab to the clinic with any guarantee of clinical application.
- Migration: Stem cell migration to areas of injury or regeneration appears to be critical to efficacy. However, migration poses a major risk for regulatory authorities, since graft size and location cannot be readily defined.
- Permanent engraftment: For brain or internal organ transplantation, treatment is permanent and the disposition of cells is 'invisible', unlike the case for skin grafting. There are limited technologies available for killing the grafts if they overgrow or become tumourigenic.
- Immunosuppression: If required, immunosuppression poses issues for a patient's well being and quality of life
- Treatment issues: Issues concerning stem cell survival or efficacy in a chronic neurodegenerative or highly medicated patient environment have scarcely been addressed in animal models.

6. Broader Concerns

- Patient expectations: The possibility of promoting recovery from conditions such as Parkinson's or Huntington's disease, for which there is either no current treatment or existing treatments are palliative and carry adverse side effects, has stimulated patient hope and demand on an unprecedented scale. Agencies developing stem cells are inundated with pleas for treatment, in part resulting from over-optimistic estimates of progress. However, progress towards clinical trials has been slow, largely due to the uncertainties about what safety and regulatory standards should apply. when they are eventually tested in clinical trials, stem cell grafts, like many pharmacological treatments before, might not fulfil the promise shown in preclinical animal studies. Even so, it is worth bearing in mind that every patient who suffered from increased dyskinesias in the Denver/New York PD transplant trial said that the benefits were worth it – they would do it again.

- Patient consent: The possibility of applying stem cell therapy to severely affected patients with, say, Alzheimer's disease raises concerns about patient competence and consent.
- Regulatory requirements: Because stem cell therapy is novel and untested, it poses severe problems for regulatory authorities and requirements may be unusually stringent.
- Efficacy: Measurement of efficacy in recovery from neurological disease is notoriously difficult, not least because of baseline decline. Is recovery measured by improvement or non-worsening of the condition? How can measurements be standardised across different centres?
- Graft survival: Unlike drug levels that are readily measurable in blood sampling, the presence of grafted cells can only be determined by surrogate markers. Imaging will provide key tools: PET to determine increases in metabolic activity, angiography to look for increased vasculature, MRI to detect graft mass and fMRI to associate efficacy with graft growth and disposition. However migratory and integrative stem cells provide a unique challenge to imaging techniques, since they form no mass and labeling of cells with a paramagnetic contrast agent would not be permissible for patients.
- Financing: While much of the demonstrations of stem cell potential in animals has arisen from academia, the development of these lines into clinical products must arise from a commercial/industrial perspective. Many academics perceive product-driven stem cell development as negative to full scientific evaluation of the stem cell approach. However, it is in nobody's interest to push stem cells into clinical trials without all the issues raised here and elsewhere on safety and efficacy being properly investigated.
- Who gets the grafts?: Unmet clinical need in neurodegenerative disease, stroke and brain injury is overwhelming and accelerating with medical treatments that keep people alive for longer. In Alzheimer's alone, 5% of the population aged 65 is affected, rising to 20% by the age of 85. Stem cell therapy offers the potential for mass treatment that may improve quality of life and reduce burden of care for millions. Nevertheless hard choices need to be made. Will priority be given to the severely demented to produce marginal improvements that reduce the expense of care requirement but not significantly enhance the patients' quality of life? Or will it be given to younger victims of stroke or traumatic brain injury that are managing reasonably well in the hope that they will recover their former abilities?

Position paper

Dr. Seppo Vainio, University of Oulu, Finland

Cellular production of Wnts, secreted growth and differentiation factors and their use as coordinators of organ specific stem cells (QLRT-2000-01275)

Embryonic stem cells (ES) and the cells of an early embryo are capable of differentiating into multiple cell lineages to form the structures of the adult individual. It is typical for the embryonic cells that their differentiation is channelled via multiple cell and tissue interactions. These interactions lead to establishment of the various cell types of the body but the molecular mechanisms how this channelling occurs is not well understood. It is also likely that embryonic organs consists of cells that full fill the criteria of a stem cell but this has been demonstrated to be the case only in limited number of situations. In order to be able to work with the stem cells the sites of their production in the embryo and the signals that regulate their growth and self-renewal need to be identified.

Wnts compose a multigene family that encode secreted factors mediate cell-cell and tissue interactions and control cell behaviour in a various ways. Wnts bind to their cell surface frizzled receptor and trigger signal transduction cascades (for details see http://www.stanford.edu/~rnusse/wntwindow. html). Gene targeting experiments in the mouse suggest that Wnts or TCF-1 as their target gene are involved in controlling differentiation of the ES cells, T cell, gut and kidney. We aim to express the Wnts in their biologically active form, to develop diagnostic antibodies against Wnts and to test their potential in maintaining stem cells of the model organs. In particular, we aim to drive the mouse ES cells towards neuronal fate with the Wnts produced. As the mouse ES cells can be cultured it would be a benefit to be able to generate a number of neuronal cells. Wnt-3 is a sufficient *in vivo* signal to regulate mesoderm formation and muscle induction *in vivo*. Hence, Wnt-3 may induce muscle from precursors in the embryo and it is also a candidate inducer of muscle from ES cells. We will generate protocols to obtain muscle precursors *in vitro*. In the kidney Wnt-4 is essential and sufficient regulator of tubular fate. Its function in maintaining pretubular stem cells will be tested. *Tcf-1*, is a Wnt target gene that is required for thymic lymphocyte stem cells to grow and self-renew. The extracellular components of the Wnt pathway in maintaining this state will be identified.

Position paper

Dr. Giulio Cossu, Universita di Roma, Italy

Stem cell therapy may be defined as a form of cell therapy that, thanks to the use of self-renewing (stem) cells, promises to lead to a definitive tissue repair. On a general basis, it can be stated that we need stem cell therapy, as any new perspective therapy that may help with as yet untreatable diseases. No one can seriously say, based on current knowledge, how useful stem cell therapy will be; of course we need to know much more about these cells before we can predict with confidence the future outcome of this kind on novel therapy. Yet, it should be stressed that bone marrow transplantation and skin graft in large burns represent examples of life saving therapies that are in clinical practice since decades and are successful because they have been utilising stem cells.

As for the possible sources of stem cells (adult, cord, embryos) all the possible sources should be explored. Imagine that a group of explorers are at the base of a mountain and want to get to the top but have no idea of how to get there. Many tracks are present but no one knows which will be the easier and/or faster to the top. Common sense would suggest that every track is explored by different explorers, thus increasing the chance to get to the top. Precluding exploration of many of these tracks is a short-sight decision. If later a track leads to a dead end or to a dangerous step, it will be abandoned, but other tracks may lead to the top. This strategy will be possible only with an adequate task force and therefore the efforts of the EC to go in this direction are most appropriate. European networks, banks, database and reagent exchange on a European basis will be needed to remain competitive with respect to US research.

This strategy should include human embryos for scientific and ethical reasons. While most of the work will be obviously carried out on mice, we know since decades that human cells are different from their rodent counterparts, if not else because they are far more difficult to expand and immortalise, quite a crucial matter for stem cell research.

At present research on cord or foetal cells is considered feasible and indeed is conceptually equivalent to organ transplantation from a cadaver. Research on embryo-derived cells is the hot point for ethical issues. These issues are treated with great wisdom in the Document by the European Group on Ethics in Science and new Technologies. It may just be added that the Italian Committee on stem cells reached different conclusions: it did not recommend use of the surplus embryos from IVF, despite the fact that they usually trashed in all the private laboratories and that no register exists in Italy. This fact indicates that the catholic influence was obviously very strong within the Committee.

On the other hand somatic nuclear transfer, in principle the procedure of choice to avoid immune problems, still faces so many technical problems that its extension to humans appears at least pre-mature.

In conclusion, while many scientific, ethical, and political issues remain to be addressed in stem cell research, it is likely that stimulating basic research on stem cells will soon lead to a better knowledge of their features and potency, and in turn will make it simpler to predict the medical, social and ethical impact of this work on the Society at large and on the bio-medical system in particular. As in other cases, the self-discipline of scientists, together with a constant observation of the funding agencies will represent the simplest and most effective way to maintain this research into a track leading to beneficial results and preventing deviations and abuses.

EU project « Biomechanical Interactions in Tissue Engineering and Repair »
'BITES' QLK3-1999-00559

Prof. Alicia J El Haj, Keele University/North Staffordshire Hospital, United Kingdom

STEM CELL RESEARCH AT EUROPEAN LEVEL

In this report, we refer to adult and fetal stem cells and will predominantly limit ourselves to considering connective tissues such as cartilage and bone as this is the basis of our EU programme.

The current debate within our field and in this project is based around the use of primary derived cells from an alternate site to the repair site of the patient (autologous), the use of adult stem cells from the patient (autologous) or the use of fetal embryonic stem cells (allogeneic).

Within our EU programme grouping, we currently have surgeons from hospitals where cell therapies are in clinical practice which use autologous cells derived from cartilage or bone from alternative sites to the repair sites, in particular Autologous Chondrocyte Implantation (ACI) .Our approach has been to tailor our research with the clinical need as a key part of the discussions.

The clinical and scientific key issues which we have raised are:

- There is a trade off in regenerative medicine between added value and improved patient outcome versus potential secondary problems which may cause a greater risk than the initial condition

- It is a fact that cartilage and bone repair in the majority of cases is not life threatening therefore choice of treatments are more likely to be conservative

- The use of autologous cells from other sites is now proving successful and any changes to other sources such as adult stem cells or fetal cells must be driven by better outcomes or reduced costs

- The key advantage of using marrow mesenchymal cells is the ability to obtain a greater number of cells from the patient which would enable scale up and engineering of other limb joints – such as the ankle or shoulder

- The risk of infection in the donor site has been realised and if 'off the shelf – allogeneic stem cell' products were available to reduce the number of operative procedures or risk of infection then this would potentially be an advantage.

The use of adult and embryonic stem cells

- The primary concern, and this is a fundamental one, is that a lot of basic scientific information is lacking about fetal stem cells and indeed marrow stem cells**.** The level of this research is based at the stage of primary biomedical research

- At RJAH Orthopaedic Hospital, a member of our consortium, we have established a cell culture facility which is used for growth and proliferation of cells for use in cell therapies. This is ISO 9002 accredited with strict guidelines and protocols. Our in house service would not cater to foetal stem cell treatments but could provide marrow banks for use by other hospitals and we are exploring this currently.

- Our cell production would involve using adult stem cells, such as bone marrow stromal cells, as more is known about controlling cell phenotype, particularly differentiation into connective tissues

- However removing bone marrow stromal cells is not a trivial operation and can be a postoperative painful procedure

Key issues have arisen regarding Regulatory Issues:

- There is a clear need for European and international regulation and guidelines for quality/safety assessment and reference protocols for establishing cell therapy units.

- We currently hold an EU Concerted Action called EUROCELL which links Autologous Chondrocyte Implantation clinics across Europe. If we are to transfer cells between units then guidelines are essential. The facilitation must be a common code of practice.

What are the economic and social perspectives for stem cell therapy?

- The British NHS perspective on these new therapies are that they must be affordable. In our hands, we have established our own cell therapy unit as this process is cheaper than buying in the commercial treatments from the industrial supplier, Genzyme.

- Industry will play a key role in the support of this treatment but the issues related to patenting of ES cells have yet to be fully resolved satisfactorily.

Communication with the public is essential both in terms of dissemination of research information and also awareness of the basis for these clinical treatments.

POSITION PAPER ON THE USE OF STEM CELLS IN « Spare Parts » project

Opinion Paper on Stem Cell Research
(Requested by the European Commission, Fifth Framework program, QoL)

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From tissue Engineering point of view, stem cells represent an attractive scientific option to enable using them to generate lost/diseased tissues.

As regards bone and cartilage tissue engineering, autologous (patient's own) mesenchymal (stromal) stem cells are easy to obtain from the bone marrow of the patient. This will obviously obviate the need for harvesting bone or cartilage biopsies to obtain cells that are needed to propagate and seed on scaffolds in order to obtain 3D-tissue constructs which will subsequently be transplanted to defective tissue. This concept of using stem cells in therapeutic tissue engineering seems attractive from theoritical point of view. From practival point of view, treatment of bone defects has been practiced for long to include using bone autografts. Autografts may contain stem cells in their marrow spaces and there should be no problem for these mesenchymal stem cells to be used for bone tissue treatment. Isolated and propagated bone marrow-derived stem cells have been also studied by one of the partners in this project to treat experimental animal long bone defects. These cells, combined with coral scaffolds have lead to favourable results.

For cartilage tissue engineering, the concept of using stem cells is relatively new and we are exploring the possibilities of using these cells to construct cartilage. Drilling was practiced to treat carilage defect treatment and this leads to to limited repair of hyaline cartilage by fibrocartilage. Stem cells that may have orginated in the bone marrow and found tehir way through these drill holes to populate cartilage defects may have been responsible at least in part for the repair of cartilage defects. Hence, the use of stem cells to regenerate cartilage can not be ignored and has to be explored for the benefit of patients in terms of improved modes of treatment.

The need for stem cells, in our project, arises from the fact that the need for tissue grafts, or procedures associated with more morbidity (e.g. cartilage) can be replaced by easier-to-access, less-complicated source of cells, i.e. bone marrow. Tissue engineering concept is based on the avoidance of bone grafts and tissue replacement alloplastic materials. It is based on using cells/cell source and biomaterials that serve temporary support/transport/(ICM) function and then absorbed by the body and replaced by native (normal or near-normal) tissue. Avoidance of grafts and replacement materials will lead to avoidance of their limitations, problems, risks, and costs.

These progenitor cells (mesenchymal stem cells) need thorough research to look at their controlled differentiation into cartilage. Factors as in vitro and in vivo microenvironment, type of scaffolds, vascularity, etc. have to be adjusted to arrive at sound conclusions and successful clinical application in treatment of cartilage tissue.

Results obtained from small animals on short term-basis can not always be met with similar successful results in larger animals or in clinical life. Hence, we have in our plan included both big animals as well as a pilot clinical study to examine the outcome of using various methods of treatment of bone and cartilage defects and arrive at better conclusions.

Ethicaly, the use of autologous progenittor (bone marrow-derived mesenchymal stem cells) should have no problem. Concerning safety, standards for in vitro methods characterization and standardisation is of great imprtance and this will help developing regulations and obtaining approval for clinical use of tissue engineering products based on this autologous mesenchymal stem cells and biocompatible scaffolds. The inetgration of stem cell-based cell therapy and biocompatible bioabsorbable scaffolds to achieve successful therapeutic tissue engineering is attractive advance but it still needs to be financed, regulated and demonstrated on EU level. We need to built stem cell research on EU level to help developing networks of scientists and experience that very much will help transfer the knowledge obtained in one field to other fields.

Risk-benefit weighting is needed where and for what indication stem cells can be used. Scenarios include risk of obtaining cartilage biopsy from the knee to treat knee cartilage defect or bone marrow cells from iliac crest. Obtaining cells from the head of femur that is discarded during hip replacement to use them for treatment of knee cartilage defects is a justified procedure. Future economical assessment based on long-term results may very well indicate the superiority of tissue engineering therapeutic methods over current joint replacement procedures.

In conclusion, bone marrow-derived mesenchymal (stromal) stem (progenitor) cells are of value in tissue engineering of bone and can also be of value in treatment of cartilage defects. Use of these autologous (patient's own) cells should raise no ethical problems. Safety and practice regulations should be observed and standards for tissue-engineering at EU level should be developed.

In utero Stem Cell Transplantation: Towards a European Perspective

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Preamble

The recognition of the utility of haematopoietic stem cells (HSC) for transplantation has been one of the landmarks of medical research during the twentieth century. For example, the harvesting and use of autologous HSC has enabled safe transplantation into patients who are immunocompromised due to the nature of, or therapy for, their disorder.[1] Because stem cells can repopulate all haematopoietic lineages, only a relatively small volume of transplant material is required in each case and these cells have the potential to sustain this *de novo* haematopoiesis over a long period. Methodologies for collection and harvest of HSC have been refined over the last decade and stem cell banks are now a reality in European centres. There are networks to assess quality control of the harvested HSC product and as the necessity to transport cells across national boundaries, for therapy in patients remote from the site of donation becomes common practice, this aspect of the process becomes ever more important.

In utero transplantation (IUT) of stem cells has been used to address problems of therapeutic intervention in those inherited haematopoietic disorders which can be diagnosed in prenatal life.[2] In many instances where family history indicates, or when there is an index case, prenatal diagnosis can accurately detect a genetic defect (and perhaps offer a prognosis) within the first trimester of a pregnancy. Transplant of HSC early in gestation exploits the immunological naiveté of the fetus so that there is no requirement to use closely matched tissue. Also, therapy can be offered before the pathological sequelae of a disorder become manifested.[2] To date, around 35 IUT procedures have been performed worldwide and the majority of these have been in European centres.[3] The most successful outcomes have been in (fetal) recipients diagnosed with an immunodeficiency disorder[3], prompting suggestions that the fetal immune system is indeed competent with respect to recognition of foreign tissue. IUT procedures performed where the recipient has been diagnosed with a haemoglobinopathy have, in general, been unsuccessful although there have been individual case reports where some engraftment has been demonstrated. In some quarters, the poor engraftment demonstrable after IUT for haemoglobinopathies has reinforced the contention that fetal immune responsiveness is the main impediment to success for this therapy. [4]

Current perspectives

The number and type of IUT procedures performed has opened debate on the utility of this therapy and its potential use for those diagnosed with a genetic disorder in prenatal life. Where the disorder is potentially life threatening *in utero* (or could lead to severe disability in postnatal life), there is an option to terminate the pregnancy. Ethical requirements dictate that it is only when a couple opt to continue with a pregnancy (perhaps for religious or cultural reasons termination cannot be a consideration) then IUT can be offered as an 'experimental therapy'. The sources of HSC for such therapeutic intervention have included: umbilical cord blood, "mobilised" peripheral blood, bone marrow and fetal liver.[3] In many cases, the source has been dictated by the dogma that closely matched tissue is safer, so paternal or maternal HSC have been the cells of choice in many cases. There are reports of fetal liver-derived HSC being used for IUT, with remarkable results.[5] Fetal liver has many advantages as a source of HSC: stem cells are more numerous in this tissue than in other sources, they have a greater proliferative capacity and in they are more robust (will withstand frozen storage without detriment).[6] It is possible that fetal liver-derived HSC can

provide enhanced levels of engraftment because these cells will home to the fetal liver in a recipient and seeding in this organ is important because it is the main site of haematopoiesis throughout gestation.[7] Use of fetal liver as a therapeutic material carries an ethical burden which can be difficult to reconcile in situations where IUT is being offered as an alternative to termination of the pregnancy. The tissue is not easy to obtain and unlike, for example, bone marrow it is not possible to obtain repeat samples if required. Nevertheless, the utility of fetal liver-derived HSC has prompted some workers to investigate the biology of these cells with a view to studying the molecular mechanisms which guide their fate[8] and to seek ways to modify HSC obtained from less ethically contentious sources so that a comparable product could be provided.

Further impetus has been given to *in utero* therapy by the prospects for using gene therapy in this setting.[9] As a therapeutic modality, gene therapy has tantalising prospects[10] but its application *in utero* is some way off. For 'conventional' IUT, harvested stem cells are introduced into the fetal recipient and ideally, the pregnancy left to continue (although fetal blood sampling is advocated at intervals, by some centres, to determine engraftment status – arguably an unnecessary additional risk to the pregnancy). For *in utero* gene therapy, cells obtained from the patient (i.e. the fetus) are exposed to an appropriate vector *in vitro*, to import the gene construct of interest, then re-introduced into the fetal recipient. The problems of appropriate levels of engraftment pertain just as much in this situation as in IUT using unmodified donor HSC. However, *in utero* gene therapy remains an attractive option due to the use of 'self' cells as the transplant vehicle but the ethical issues require to addressed before this treatment modality can be contemplated.

In the current climate and with IUT still in its infancy, there is a need to share data obtained from the cases thus far performed. Importantly, it is imperative that we begin to build a picture of what types of disorder might not be amenable to IUT and this issue must be addressed by reference to the science underpinning clinical practice rather than by a succession of failures in the clinic itself.

Remit of the ENFET Consortium

These issues have been the driving force for the ENFET Concerted Action and have brought together groups throughout Europe (and in Israel, as an associate member) to collate and to evaluate evidence obtained from IUT procedures thus far performed. Each of the European groups which have carried out an IUT procedure is represented in the consortium. In addition, there are representatives from those institutions which are involved in research into the biology of haematopoietic stem cells. This crucial partnership resolves to bring together both scientists and clinicians so that relevant data derived from laboratory-based studies can be used by clinicians in decisions regarding the option to use IUT as a therapeutic stratagem. We have also incorporated interests in the field of gene therapy, since this issue must be debated as advances in our knowledge continue. Further, there has been some lobbying in the US to use gene therapy as an *in utero* strategy[11], although this approach has not yet been realised. Therefore, it is an important aspect for the ENFET consortium to embrace all forms of *in utero* therapy so that a Europe-wide consensus can be promulgated by the end of this Concerted Action programme.

There are a number of concerns regarding therapy *in utero* using haematopoietic stem cells. Firstly, stem cells *per se* have been regarded as the 'mother of all cells'[12] and thus, as the obvious choice for the transplant vehicle in a number of genetic disorders. However, we now understand that stem cells are capable of not only multilineage development/commitment in a haematopoietic context but also 'plasticity', i.e. the ability to seed within non-haematopoietic tissues and therefore to have potential for repopulating other tissue/organ systems and generate non-haematopoietic cell lineages.[13] This appreciation of the diverse nature of stem cell potential has prompted a reappraisal of the therapeutic potential of stem cells. Although we have been concerned about the range of

disorders amenable to IUT using HSC, we might – if the data currently being generated support the contention – widen the horizons to include a much wider variety of disorders which can be diagnosed before birth. The list could include metabolic disorders (e.g. storage diseases) which have currently not enjoyed successful outcomes following therapy using IUT.[8] However, despite the enthusiasm with which these new developments in our understanding of stem cell biology have generated, there remains some doubt in many quarters that IUT will be the panacea for all inherited disorders. There is much to be learned about stem cell plasticity and the prospect that other types of stem cell are required to provide a wider dimension to *in utero* therapy remains to be fully explored.

Regulatory Issues

The UK is moving towards a regulatory framework for all tissue banking, where the stored tissues are intended for therapeutic purposes. This Code of Practice is to be accredited by the Medicines Control Agency (MCA) under the auspices of the UK Department of Health.[14] There is a two-year 'lead in' period and the Code will be in force by April 2002. Thereafter, all Institutions will be required to be accredited if they are to provide tissues for human therapy and the regulations will apply to stem cells as well as to solid organs. There continues to be intense discussion and consultation on issues relating to the new Code of Practice, including regular fora and workshops to bring together interested parties. Those working in the field of *in utero* transplantation will also come under the remit of the Code of Practice but there are some issues specific to this type of therapy. The donation and use of fetal liver as a transplant vehicle cannot be covered by the same regulations as, for example, donation of bone marrow. The donor of fetal tissue may provide the material for altruistic reasons but the majority will not consent to give a blood sample for serological screening (the nature and circumstances of the termination process may be too traumatic to press a donor for additional information). Thus, the tissue itself must be used for screening. It is arguable that this would provide a safer alternative to screening of the donor (since the transplant material *per se* is being tested) but such provision must be considered by the regulatory bodies if it to become a component of future *in utero* programmes in the UK, if not in Europe. The almost 'unique' nature of *in utero* therapy requires that the ENFET consortium develops a regulatory framework to cover this form of therapy so that any future Code of Practice can have Europe-wide recognition and acceptance. In the UK and elsewhere, a revision of current guidelines and regulations will be needed to cover the advent of gene therapy. The additional stages involved in preparing cells for infusion into patients in a gene therapy protocol will inevitably require a further (and possibly separate) regulatory framework. The impending UK Code of Practice can provide a useful benchmark for any future requirements.[14]

Ethical and Social Implications

The advent of novel therapies with promise of a 'cure' for disease is inevitably attended by intense media interest, which often translates into a message that the new therapy will be available to all who request it. In practical terms there are many impediments to the widespread implementation of novel treatments, including financial restrictions or perhaps that they are simply not applicable in every case. One of the conclusions to be drawn from the small number of IUT procedures thus far performed is that not all prenatally diagnosed genetic disorders are likely to be amenable to this form of therapeutic intervention. For example, IUT for metabolic disorders have not been successful but they represent such a disparate set of conditions that it would be impossible to predict which specific disorder would be a good target for IUT unless far greater numbers were transplanted and outcome data rigorously analysed. Clearly, such an approach is ethically unacceptable. As in the pioneering days of heart transplantation where, although it was hailed as a major step forward for medicine: all recipients died – there is a need to return to the basic science

before further advances can be contemplated in the clinic. This approach has been, to some extent, borne out with the current data on mesenchymal stem cells and the concept of stem cell plasticity.[13] The promise of gene therapy will inevitably stir public awareness and lessons learned from previous 'advances' in medicine must be practiced. The lack of success in the first heart transplants resulted in a moratorium on the procedure until more of the basic science was understood. The recent tragedy in a gene therapy trial in the US looks less like 'history repeating itself' rather than 'history being forgotten'. A partnership of clinicians and scientists working together to understand the biology of a system and putting into clinical practice the results of these endeavours, is a potent force for real advances in medical science.

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SUICIDE GENE THERAPY IN STEM CELL TRANSPLANTATION

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Hematopoietic stem cell transplantation from allogeneic donors (allo-SCT) is the treatment of choice for many patients with haematological malignancies, and is a novel therapeutic approach for patients affected by solid tumours. In allo-SCT donor lymphocytes play a central therapeutic role in promoting an anti-tumour effect (graft-versus-leukemia – GvL) and in providing immune reconstitution. However, their use is limited by the risk of a severe and potentially life-threatening complication: graft-vs-host disease (GvHD). We previously showed that the infusion of donor lymphocytes expressing the herpes simplex virus thymidine kinase (HSV-tk) is an efficient tool for controlling GvHD (observed in 100% of patients), while preserving GvL (observed in 66% of patients). Despite the encouraging results, three limitations were identified: 1) The partial resistance to ganciclovir (GCV) of chronic GvHD (1 pt). 2) The need of using GCV to treat cytomegalovirus disease (4 pt). 3)A strong immune response against transduced cells. The factors associated with the immune response against the transgenes were: 1)the n. of CD4 cells at the time of DLI. 2) The time between BMT and DLI, 3). To exploit the suicide gene approach to a larger number of patients, we recently designed a clinical protocol for programmed Tk-DLI for immune reconstitution and relapse prevention after stem cell transplantation from haplo-identical donors (haplo-SCT). In this clinical setting, immune response against the transgene is not expected, due to the profound immunosuppressed status of treated patients. 7 pt with high risk hematologic malignancies who underwent haplo-SCT in the presence of disease received escalating doses of Tk-DLI 42 days post SCT beginning at $5x10^4$/kg up to 10^7/kg. Infused lymphocytes were 100% CD3+, 13-50% CD4+. Circulating transduced cells were documented in 6/7 pt (from less than 0.01 to 30% of CD3+ cells). 2/7 pt reached 50 CD3+/microl by day 30, increasing steadily thereafter. 4/7 pt maintained the complete remission for over 3 months after the infusion. 1 pt relapsed in the absence of Tk cell engraftment. No acute GvHD was observed in this initial series of patients. However, 4/7 patients had to be treated with GCV to control CMV infection. This resulted in the rapid elimination of Tk cells. Three patients received a second Tk-DLI after GCV discontinuation. T-cell engraftment was documented in all pt, with a kinetic comparable to the first infusion. A pt who relapsed after GCV-elimination of transduced cells received 10^7/kg Tk-DLI and remained in stable disease. One patient received unmodified lymphocytes during GCV treatment and died of GvHD. In conclusion, Tk-DLI represents a promising tool for preventing disease relapse and promoting immune reconstitution after haplo-SCT. However, the concomitant need for utilization of GCV early post-transplantation severely limits the impact of this technology. To circumvent this limitation, new suicide systems are under investigation.

Developing Regulation for Laboratory Procedures Associated with Stem Cell Therapy in the UK: The Role of the NIBSC Liaison Group on Stem Cell Therapy

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The clinical use of haematopoietic stem cell transplantation has progressed rapidly in recent years with new research developments being transferred quickly into medical practices. The developing potential for in vitro expansion and even genetic modification of stem cells of both embryonic and adult origin heralds a second wave of technologies some of which may be brought into clinical use in the near future. These dramatic developments whilst generally welcome in that they bring new opportunities to improve patient survival and prognosis, are being introduced to a health-care community where the laboratory expertise and experience of the individual centres asked to perform the technical preparation, quality control and storage of stem cells. In the UK many laboratories are preparing to adopt the international JACIE guidelines that deal with the widest aspects of stem cell treatment. However, as a result of directives from the UK Department of Health an urgent programme of assessment specifically targeting laboratory processing of stem cells is now under way. This initiative aims to have all stem cell processing laboratories accredited under Good Manufacturing Practice guidelines within the next 18 months. The accreditation will be performed by the Medicines Control Agency using The Code of Practice for Tissue and Cell Banks (Department of Health, 2001) as their primary guidance for laboratory assessment.

In the last two years the NIBSC has established a series of open forum meetings to allow independent and open discussion to identify aspects of stem cell therapy in the UK that would benefit from further standardisation. An active NIBSC stem cell steering group has also developed which has taken key items from the Forum discussions and established working groups of those practically involved in the relevant areas to initiate collaborative studies. Currently these working groups are dealing with issue relating to the quality and safety of raw materials used in stem cell processing and cryopreservation and storage of haematopoietic stem cells. In addition NIBSC is organising and hosting a presentations and a quality systems workshop to raise awareness and provide training regarding the new Department of Health requirements. Future NIBSC stem cell forum meetings are planned to address *in vitro* expansion of stem cells and potential therapies using non-haematopoietic stem cells.

Culture and expansion of stem cell preparations *in vitro* for clinical use opens up many more variables that could influence the outcome of therapy. The growth medium, the growth factors used to promote replication of stem cells and even the surfaces on which the cells are grown may all vary in ways that could influence the final product and potentially result in different clinical responses. Much more work is required to demonstrate that consistent in vitro expansion can be achieved in different laboratories. The response of stem cells to cryoprotectants remain to be characterized and therefore the approaches and reagents used in the process of cryopreservation and quantitation of cell composition for transplanted material for stem cell therapy are in urgent need of standardization. Further concerns relate to the tumorigenic potential of stem cell preparations and approaches need to be developed to minimise these risks in part by standardising culture conditions. Research data suggests that embryonic stem cell lines maintained *in vitro* are genetically stable for many generations and therefore present a large resource for the development of novel therapies. However, complex and critical factors are at work that need to be understood to ensure safe and effective stem cell therapy. The worldwide distribution of embryonic stem cell lines introduces the risk of variation in cultures as they are passed from

one laboratory to another. Thus it is vital to have fully characterized cell banks of these lines prepared and validated to provide a reproducible and qualified source of cells.
Stem cell therapy in general will benefit significantly from technical standardisation to develop common good practices. Furthermore, considerable efforts will be needed to standardise culture conditions and reagents to assure a reproducible and safe outcome for the therapeutic use of cultures expanded *in vitro*.

Ethical and regulatory issues in stem cell research
Joint position paper

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Introduction

The purpose of the EUROSTEM project is to give an exhaustive analysis of the ethical, legal and social aspects of human stem cell research and stem cell therapies in Europe. The project has not yet started and it would therefore be premature to present any conclusions. In the following we will therefore merely outline the main ethical and regulatory issues that the project will analyse, and point out where the issues of ethical contention are located.
The purpose of the EMPIRE project is to analyse how empirical research results are used in arguments in bioethics and in legal regulation of bioethical issues. One of the areas that the project is looking at are the current debates about the regulation of stem cell research. In these debates the future therapeutic potential flowing from stem cell research plays a very large role, and this raises interesting questions about how to deal with scientific uncertainty in ethical arguments.

Ethical issues in stem cell research

Many human diseases are caused by the loss of specific types of cells, or are accompanied by such loss. If these cells could be replaced it would create a very exciting new range of therapeutic techniques for some of the major diseases plaguing the modern world. The list of diseases where such an approach is a theoretical possibility is long and includes among others:

Parkinson disease
Alzheimer disease
Diabetes (type 1)
Heart failure after myocardial infarction
Liver failure
Osteoarthrosis
Bone marrow failure

The discovery that human stem cells can be grown in tissue culture and differentiated into the desired type of cell has made the introduction of cell replacement therapy for at least some of these diseases much more likely.
There is agreement among all participants in the ethical debate that the aim of stem cell research, i.e. the eventual cure or alleviation of human disease and suffering is a good aim. The disagreement centres on whether some of the ways in which we can produce stem cells are so ethically problematic that they should not be pursued, even if this would slow down or prevent the development of cell replacement therapies for some of the diseases where replacement therapy is a theoretical possibility.

Stem cells can be derived in a number of ways:

1. Adult stem cells, including stem cells from cord blood
2. Fetal stem cells
3. Embryonal stem cells

From spare embryos
From specifically produced embryos
Produced without cloning technology
Produced with cloning technology
4. Stem cells cloned without involvement of embryos

Seen from a technical point of view the ideal stem cell for cell replacement therapy would display a number of characteristics:

1. No immunological rejection
2. Immediate availability
3. Availability in large numbers
4. Controlled differentiation to desired cells
5. Controlled integration into existing tissues and biological niches leading to normal function
6. No other biological risks

These characteristics are fulfilled to a different degree by stem cells derived in different ways. The immunologically optimal stem cell with no rejection problems, would be a stem cell that is immunologically identical to the recipient, and such a stem cell can (at present) only be obtained either by using cloning techniques or by deriving adult stem cells from the recipient him- or herself.
In the ethical discussions about stem cell research it is possible to identify a "hierarchy of controversy" in that some ways of deriving stem cells are seen by some commentators to be more ethically problematic than others:

1. Cloned embryonal stem cells
2. Specifically produced embryonal stem cells
3. Embryonal stem cells from "spare" embryos
4. Already established embryonal stem cell lines
5. Adult stem cells

This hierarchy of controversy mirrors three underlying ethical controversies. The first of these is whether destructive research on embryos, or any other destruction of embryos is wrong in itself because embryos have significant moral status. This controversy is very old and also occurs in the debates about abortion and about assisted reproductive technologies. The second controversy centres on whether there is a problem in producing embryos solely for the purpose of destructive research (or in the future derivation of stem cells leading to the destruction of the embryo). This question has previously been discussed extensively in the context of whether or not research into assisted reproduction should only use so-called "spare" or "supernumerary" embryos, or whether it would be acceptable to produce embryos purely for research purposes. The third controversy relates to the debate about reproductive cloning. If reproductive cloning is ethically problematic, and if cloning of embryos for the production of stem cells solves some of the technical problems involved in cloning humans, then there might be a technical slippery slope from therapeutic cloning to reproductive cloning.

The more of these controversies a specific method for producing stem cells actualise, the more heated will be the debate about its ethical status. There are arguments to show that none of the controversies involve real ethical problems, and that all of the methods for producing stem cells outlined above are ethically unproblematic and should be used because of the large possible gains in the form of new therapies. But there are on the other hand also arguments to show that the ethical problems are real and that only some of the methods are acceptable.
At the present time there seems to be no hope for a quick resolution of these disagreements.

For some types of stem cells we could envisage the establishment of stem cell banks or repositories of stem cells with a range of tissue types ready for use in situations requiring immediate treatment. Such banking of stem cells raise specific issues about 1) ownership of the cell lines, including ownership of intellectual property and patentability of cell lines, 2) access to the cell lines and 3) whether such banks should be organised as part of the public health care systems. These problems are important in themselves, but not central to the ethical debates about stem cell research as such.

Some uses of stem cells involves genetically modifying these cells before they are implanted in the recipient. This raises a number of issues related to the more general debates about different types of genetherapy.

Regulatory issues
A basic assumption of the EUROSTEM project is that a European analysis and response to the new possibilities that stem cell research opens is needed.
We cannot import regulatory solutions from elsewhere, since such solutions will have been subject to the vagaries of the political process in the country in question (e.g. the American regulation of stem cell research depending on the result of the last presidential election). And we cannot wait for large-scale international agreements that may take years to reach.
Seen from a research point of view we are also in the enviable position that Europe itself is likely to act as a kind of regulatory laboratory with different countries implementing different kinds of regulations of stem cell research. These regulations are likely to differ in many ways, and will almost certainly differ with regard to what types of stem cell research that will be allowed. The UK has already allowed stem cell research using embryonic stem cells from specifically produced and cloned embryos, but other countries in the EU are unlikely to implement equally liberal regulations. These differences between countries constitute a "natural experiment" and can be exploited for research purposes.
Although it may be fanciful to believe that one common regulatory scheme could be implemented across the EU member states (and future member states), there is no doubt that it will be possible to draw important common lessons by studying the developments in the different countries and highlighting "good" and "bad" practice both with regard to public participation in the debate and with regard to regulation.
In this context it is especially important to analyse 1) whether the problems that are currently prominent in the debate are really the most serious and difficult ethical and legal problems, and 2) the "hidden" side-effects of different regulatory schemes.
Once regulation allowing specific types of stem cell research is in place it will become important to monitor how the regulatory measures are working and what types of stem cell research actually takes place. The purpose of such monitoring is twofold 1) to assess the effectiveness of the regulatory system, and 2) to assess whether the kind of research pursued is along the lines of the "promised researched" used as arguments for allowing specific types of stem cell research in the public debate.

One fairly obvious point can be made about regulation without prejudging the further analysis performed in the EUROSTEM project. If a jurisdiction already allows and/or funds research using human embryos for some purposes it will be very difficult to mount arguments that stem cell research using the same types of embryos should not be allowed and/or funded. If, for instance, a jurisdiction allows research on "spare" embryos with the purpose of improving in vitro fertilisation techniques it is difficult to see any good argument for not allowing stem cell research using "spare" embryos, given that all agree that the aims pursued by stem cell research are good and important aims[7].

[7] This does not exclude the need for assessment on each individual project with regard to its scientific methodology and ethical implications.

Embryonic Stem Cell Research at European Level: Legal Limitations on Research and its Results?

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1. Introduction

1. The chances for research, experimentation and new therapies involving human embryos and foetuses have shown not only divergent positions, but indeed tensely confronted ones, particularly since it has been proved how versatile and flexible embryo cells are for the development of specific cellular lines to be used for therapeutic transfer into humans.

In fact, facing the promotion of freedom of research by some authors and, through it, of the scientific development that will benefit forthcoming generations and probably present ones as well, on the other hand we have the opposite criteria consisting of comprehensive protection of the human embryo and foetus by means of a specific legal status.

2. The legal issues that research and experimentation on implanted or expelled embryos and foetuses pose, are not completely new[8]: such activities have already been faced with certain treatments and techniques which results were very beneficial for other foetuses and persons. Nevertheless, the need to establish some control and regulation of these particular procedures quickly arose, with the purpose of avoiding risks and manipulations of the living foetus during pregnancy that could cause malformations apparent after birth. What has been also very important is legal assessment and treatment of the experimentation carried out on human foetuses, which were extracted alive by surgical means, in cases of legal abortions.

3. Nowadays, scientific interest is focused on the utilisation of *in vitro* human embryos, in the light of the promising possibilities that are opening up for new ways of treating of certain illnesses from stem cells[9]. Without any doubt, the ethical confrontation towards this eventuality is even more intense, if that is possible, and the legal questions are equally greater. These cells are also found in other biological sources (aborted foetuses, amniotic liquid, umbilical cord, as well as stem or somatic cells of adults). However, the legal problems that arise in relation with these other sources than embryos are not new so far they don't pose specific controversies and, in most cases, can be successfully solved through the laws regulating the utilisation of these biological materials for research[10]; in the event of clinical trials the laws regulating such activities in almost all European countries will be applicable, and will soon have to be updated as a consequence of the recent approval of Directive on good clinical practices concerning clinical trials of medicaments for human use[11].

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[8] See on the matter, ie, the Spanish Law 42/1988, of 28 December, on the use of human embryos and foetuses, their parts, tissues and cells.

[9] See further Robin LOVELL-BADGE, *Stem cell therapy: the potential importance of research into 'therapeutic cloning', embryonic stem cells and adult stem cells*, in Minou Bernadette FRIELE (ed.), "Embryo Experimentation in Europe", Europäische Akademie, Bad Neuenahr-Ahrweiler, 2001, pp. 32 ff.; National Academy of Sciences, *Stem Cells and the Future of Regenerative Medicine*, National Academy Press, Washington, D. C., 2001.

[10] See Directive 98/79/EC, of 27 October 1998, concerning in vitro medical devices.

[11] Directive 2001/20/EC, of the European Parliament and Council, on 4th April 2001.

Given that some of these objectives and procedures related to stem cells could be confronted to the juridical protection of the *in vitro* embryo, according to which, however, unanimous criteria in relation with at least these objectives and procedures do not exist, I think it will be more useful for this presentation to concentrate myself on the specific legal problems related to *in vitro* human embryos by research.

4. The first relevant question to be solved should be what does mean human *in vitro* embryo for our societies, how should be its moral and juridical status, what kind of values are embodied by embryo; i e, is dignity a quality of human embryo? However, I think that it should be a very hard and ambitious task too much to try to solve this question in this short presentation; but it is also true that we will be able to realize indirectly it, as a result of the legal comparative approach I will do, which could reveal in some way how is this social perception of *in vitro* embryo in some relevant EU Member States.

On the other hand, we cannot forget that, in order to carry out a correct legal analysis, it is very important to point out that at present scientists are dealing only with very promising laboratory research, that still has not given place to any therapeutic applications in humans (apart from some isolated clinical trials on bone-marrow and embryos to obtain hematopoietic cells). This means that, at present (taking into account that developments of this research are going very fast), the effective treatment of a person with a serious pathology or malformation is not possible still through embryonic stem cells. Consequently, the current problems are focused on the legal assessment of the use of the human embryo as a material or means for research and experimentation. Nevertheless, this should not hinder consideration of legal perspective as regards the future possibility of these techniques developing correctly and ultimately constituting effective treatment for human beings; consequently, from a legal point of view, we also have to attend to the analysis of the creation and the use of human embryos as sources of therapeutic biological materials.

It is also useful to clarify that in my opinion there are not relevant connections between the use of in vitro embryos for research and the right to reject pregnancy. The different biological situation of embryo in relation to the implanted foetus as well as the different interests that could be in collision give us some arguments that need to be developed.

2. The lack of a legal consensus in the European Framework

The following statement only intends to provide a brief but sufficiently illustrative description of the legal solutions that exist nowadays, and which reveal the lack of minimal points of consensus –so different are the legal systems from country to country that have already been established or are in process of being approved-, but at the same time they suggest there is a need to reach meeting points in this matter.

For this presentation we will pay attention to some European representative approaches[12], as they are very different from one another and illustrative enough to show us this lack of consensus in Europe from a legal point of view. It is worth to emphasize that notwithstanding these different focuses all legal state approaches do not exclude serious

[12] For a more extensive approach concerning the existing regulations in Europe on human embryo research see further European Group on Ethics in Science and New Technologies to the European Commission, *Opinion No 15 on Ethical Aspects of Human Stem Cell Research and Use*, of 14 November 2000; Minou Bernadette FRIELE (ed.), "Embryo Experimentation in Europe", cit.

infractions of law to be considered as a crime and to punish them with a penalty of imprisonment. These countries are: United Kingdom, Germany, Spain and France[13].

2.1. Disparities in Comparative Law

1. **United Kingdom** was the first country to adopt a legal decision that allows research into human embryos –clones or not- directly created for specific research purposes in this line of therapies from stem cells and for other[14]. For this purpose, the British Government entrusted an independent Commission (chaired by the Chief Medical Officer), created for the unique objective of evaluating the chance of modifying the current legislation on the matter[15]. The Commission issued a report[16], which moved towards an affirmative main question: it recommended that research using embryos (whether created by in vitro fertilisation or cell nuclear replacement) to increase understanding about human disease and disorders and their cell-based treatments should be permitted, subject to controls in the Human Fertilisation and Embryology Act 1990.

Consequently, by initiative of the Government, the Parliament approved the modification of the Act 1990[17], which was formed by the introduction of a new text: The Authority may issue licence for research under paragraph 3 of Schedule 2 to the Act for any of the following purposes: a) increasing knowledge about the development of embryos; b) increasing knowledge about serious disease; or c) enabling any such knowledge to be applied in developing treatments for serious disease.

As it can be seen, we are really dealing with a legal enlargement that extends the previous legality of the creation of human embryos (by sexual reproduction, that is, with fertilisation of two gametes, male or female, or by cloning), in order to start up certain research lines that were not allowed before and could not for this reason, receive the appropriate permit of Authority (until that date, law only provided the authorisation of research aimed at the objectives quoted in section 2 of paragraph 3 of the named Schedule 2). I have to remark that the revision of the law does not mention the effective application of the future therapies with patients (controlled trials), nor the use of human embryo cells as therapeutic materials. Neither does it modify previous regulation on reproductive cloning, whose prohibition as an offence remains still in its initial terms.

2. In the **German Federal Republic**, the Embryo Protection Act of 1990[18], has been indirectly in charge of this matter, but with sharp remarks in its determinations, such as the following: 1. To forbid the creation of human embryos with any other purpose than human procreation (art. 1, par. 1.2, 1.5 and 1.6; art. 2). 2. To prevent the situation arising of having supernumerary embryos from medical assisted reproduction techniques, preventing in an indirect way human embryo cryopreservation (art. 1, par. 1.4 and 1.5). 3. The prohibition of creation of human embryos by cloning, whatever the aimed purpose: reproductive or having other purposes other than human reproduction (art. 6).

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[13] Italy is a very particular approach, given that at present no Law on the matter has been approved by the Italian Parliament, even that some Bills were discussed. It means that from a legal point of view, Italy is nowadays the most liberal country in Europe in relation to Biomedical activities: by default, and according to the rule of law, there is no legal prohibition for the creation and use of embryos for research or for other purpose.

[14] See Deryck BEYLEVELD and Shaun D. PATTINSON, *Embryo Research in the UK: Is Harmonisation in the EU Needed or Possible?,* in Minou Bernadette FRIELE (ed.), "Embryo Experimentation in Europe", cit., pp. 58 ff.

[15] Constituted by the *Human Fertilisation and Embryology Act* of 1 November 1990.

[16] It is known as "Donaldson Report", that included nine recommendations in total. There were also other positions that positioned on the convenience or not of the modification of the Law in this sense; in general the coming from scientific institutions were favourable, as long as the religious ones were contrary.

[17] It was passed as *The Human Fertilisation and Embryology (Research Purposes) Regulations 2001,* of 24 January 2001, establishing its coming into effect the 31 of the same month and year

[18] *Gesetz zum Schutz vom Embryonen* of 13 December 1990.

We will briefly comment on the last assumption (embryo cloning with any purpose)[19]. With this prohibition, it was included not only the creation of children from cloning techniques, but also the creation of human clone embryos, as well as the single nuclear replacement (punishable as tentative, if that was the purpose of the author), that constitutes a crime. The expert German lawyers have raised several, non-superfluous interpretative doubts about their current legal text, such as the matter related to the sense of the word "embryo" in the article that forbids cloning (art. 6), as in another place, the law itself gives a definition of embryo to its effects ("already the fertilised ovule, being able to development from the fusion of the nucleus", art. 8), which seems to exclude the cases of transfer of a nucleus from a somatic cell into a previously enucleated ovule (nuclear transfer technique). It is argued that this ovule is not an embryo such as, taking into account that it is only forbidden by law to generate an embryo, even though afterwards it is going to become an embryo. On the whole, although it is doubtful that such a technique-legal problem really exists, as the process will unfailingly lead to the production of an embryo, the interpretative proposal is that the general embryo definition of art. 8 is not applicable to art. 6 and the word "embryo" that the later uses includes also the manipulated ovule[20].

3. Concerning **Spain**, this matter is regulated by the Assisted Reproduction Techniques Act of 1988[21]. This Law only allows the following activities concerning research with human embryos: 1. Cryopreservation of embryos is permitted by Law, which means that the possibility of having supernumerary embryos from assisted reproduction techniques is not excluded. 2. Research or experimentation on *in vitro* human biologically non-viable embryos, under certain conditions (art. 15.3). 3. When they are aborted preimplantatory embryos, they are considered dead or non-viable, and can be used for several purposes, above all research (art. 17). 4. Finally, in the case of viable *in vitro* embryos, it is allowed research if applicable to diagnosis with therapeutic or preventive purposes (in other words: for the benefit of the embryo), and if no modification of genetic non-pathologic heritage of embryo is ensured (art. 15.2)[22].

According to the Spanish Law and to the Constitutional Court[23], Spanish Constitution only offers protection to the *in vitro* viable embryo; this means that the non-viable embryo has no legal protection under the Spanish Constitution. Discussion has been focused to clarify what non-viable legally means: the broader criteria are that it refers only to a biological comprehension and not to a functional one (i e., a supernumerary embryo may be biologically competent but functionally incompetent, as it is not able to be transferred to a woman for pregnancy).

On the other hand, since 1995, the fertilisation of human ovules for different purposes than human procreation constitutes a crime (art. 161.1 of Penal Code). Without affecting the difficulty involved in determining the exact scope of this prohibition, in these terms, it does not seem legally acceptable, at least from a perspective *de lege lata.*

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[19] Accordingly with art. 6. "(1). The one who artificially will give place to the creation of a human embryo with the same genetic information that other embryo, foetus, human being or dead person, will be punished with imprisonment up five years or with a fine. (2) The one who will transfer the embryo quoted above to one woman, will be punished in the same way. (3) The attempt is punishable".

[20] See details about the argumentation in Albin ESER et alt., *La clonación humana. Fundamentos biológicos y valoración ético-jurídica*, in "Revista de Derecho y Genoma Humano / Law and the Human Genome Review", No 9, 1998, p. 369.

[21] Law 35/1988, of 22 November.

[22] See Carlos M. ROMEO-CASABONA, *El Derecho y la Bioética ante los limites de la vida humana,* Ed. CERA, Madrid, 1994, pp. 393 f.

[23] See Spanish Constitutional Court ruling of 17 June 1999, concerning a claim against the conformity of the Assisted Reproduction Techniques Act to the Spanish Constitution.

4. In **France**, the use of any human embryo with purposes other than human reproduction[24] is forbidden, under penal sanction. The prohibition entails the following conducts: 1. The *in vitro* human embryo conception with research or experimentation purposes (art. 511-18 of the Penal Code). 2. Research or experimentation within an embryo in infringement of provisions of art. L. 152-8 of the Public Health Code (*Code de la Santé Publique*)[25] (art. 511-19 of the Penal Code). 3. The creation or use of embryos with industrial or commercial purposes (art. 511-17 of the Penal Code). 4. The creation of human embryos without respecting the established requirements in articles L. 152-4 and L. 152-5 of the Public Health Code (art. 511-16 of the Penal Code). The current French legislation does not contemplate an explicit prohibition of cloning -reproductive or not-, but there is no doubt about that the so-called "therapeutic cloning" falls inside the previous prohibitions.

Anyway, provided the forthcoming revision of these Laws by the French legislator, there have already arose very important opinions about the necessity that the former –the legislator- should reconsider the keeping of the human embryo research or experimentation current drastic prohibition[26].

5. By the side of the **European Union**, we have to point out that it has no direct legislative competence to regulate research at the European level; it remains a task of the Member States. Consequently, Directive 98/79 EC concerning in vitro medical devices, refers for these matters to the provisions of the European Convention on Human Rights and Biomedicine[27].

The European Parliament has twice given a pronouncement absolutely contrary to the human beings cloning, in any level of development, even although with research purposes, without arriving to the formal prohibition of itself: Resolution of 28 October 1993, about cloning of human embryo, and Resolution 12 March 1997 about cloning.

At the moment, the European Parliament has not either maintained a definitive position about the creation and use of human embryos for research or with the purposes of obtaining biological therapeutical parts thereof, despite that in Resolution of 7 September 2000 the called therapeutic cloning is totally rejected and the States and International Community are invited to issue regulations to forbid the cloning of human beings in any phase of its formation and development[28].

The European Parliament is currently in a process of approving a new Resolution related to human genetics, but despite stem cells are quoted in two Considerations thereof, no formal position is given.

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[24] According to the rules that were established in Law 94-653 of July 1994, *relative au respect du corps humain.*

[25] Art. L. 152-8 of the Penal Code was introduced by Law 94-654 of 29 July 1994, *relative au don et à l'utilisation des éléments et produits au corps humain, à l'assistance médicale à la procréation et au diagnostic prenatal.*

[26] In this sense, the Conseil d'Etat, *Les lois de bioétique: cinq ans après,* La Documentation Française, Paris, 1999, pp. 17 ff. Concretely it stresses the need to re-examine the question of banning research on embryos and that the legislator will have to position himself on this matter, specially taking part on "the conditions where some research on the embryo could be authorised", subject to stringent rules (p. 151). Notwithstanding, it rejects the possibility of producing embryos for research as well.

[27] This Directive stipulates: "For the purposes of this Directive, the removal, collection and use of tissues, cells and substances of human origin shall be governed, in relation to ethics, by the principles laid down in the Convention of the Council of Europe for the protection of human rights and dignity of human being with regard to the application of biology and medicine and by any Member States regulations on this matter" (art. 1.4).

[28] Mention should be given to the Charter of Fundamental Rights of the European Union, approved by the European Council on 14 October 2000, which stipulates the prohibition of making the human body and its parts as such a source of financial gain, and the prohibition of the reproductive cloning of human beings (art. 3.2).

At the same time we have to recall that the European Group on Ethics in Science and New Technologies to the European Commission, has set out in several Opinions its positions on the matter[29].

6. In the **United States of America**, the National Bioethics Advisory Committee has published a report concerning research with stem cells[30]. Among its recommendations: 1. The use of supernumerary embryos remaining from infertility treatments should be eligible for federal funding. 2. Federal funding should be excluded for research involving the derivation or use of human embryonic stem cells from embryos made solely for research purposes. 3. Federal agencies should not fund research involving the derivation or use of human embryonic stem cells from embryos made using somatic cell nuclear transfer into oocytes.

Finally, we have to mention the recent resolution by the President of US on "Stem cells and protection of life", of August 2001. Although it does not have a normative range and it goes beyond the European level, without no doubt, it is going to have a great influence in the next future politics of the country in this scientific sector, where he is still the world leader.

To sum it up, they are two main ideas at this presidential resolution: 1. The existent sequences of stem cells that come from human embryos that have to be used in the public founds financed research, have to be obtained, first, with the consent of the suitably informed donors; second, from the surplus exclusively reproductive purposed created embryos; and, third, without any type of remunerative incentive for the donors. 2. The Government supports the intentions of the Legislative of forbidding the production of human embryo exclusively for its destruction during medical research.

This position has not reached unanimity among US scientific community, institutions and bodies; i e, the National Academy of Sciences has given its answer to the federal government position in a very high level of criticism: it recommends that research on both adult and embryonic human stem cells should be pursued, as well as that it is a need for the development of new stem cell lines in the future[31].

2.2 The ambiguity of International Law

1. The European International framework constitutes a reliable reflection of the disparity of normative solutions given at the moment by some of the more representative European States, in relation to the creation and use of human embryos for research.

2. The **UNESCO** Universal Declaration on the Human Genome and the Human Rights of 11 November 1997, does not take a position about the possibility of experimenting with human embryos, although rejects clearly reproductive human cloning (art. 11). It is a topic that could be pending for a future Convention, also Universal, about the same matter as the Declaration.

3. We should pay more attention to the **Council of Europe**. It had already positioned on the human embryo research and its use with scientific purposes in two former Recommendations[32].

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[29] See European Group on Ethics in Science and New Technologies to the European Commission, *Opinion No 15 on Ethical Aspects of Human Stem Cell Research and Use*, cit.

[30] See National Bioethics Advisory Committee, *Report on Ethical Issues in Human Stem Cell Research*, 1999.

[31] National Academy of Sciences, *Stem Cells and the Future of Regenerative Medicine*, cit.

[32] See Recommendations 1046 (1986), *on the use of human embryos and foetuses for diagnostic, therapeutic, scientific, industrial and commercial purposes*, and 1100 (1989), on *the use of human embryos and foetuses in scientific research.*

3.1. Recently this Institution has accepted a more or less open solution in the *Human Rights and Biomedicine Convention* of 4th April 1997, as there has not been a wide consensus to this respect in the European framework; contrary to this, it was one of the most argued matters and, probably, the most important cause because some more representative European States have not still signed or ratify the Convention (the German Federal Republic and the United Kingdom, in the first case, and France and Italy, in the second one). The experimentation with *in vitro* embryos is gathered in Chapter V, dealing with "Scientific Research". Nevertheless, it is true that the Convention should take into account the possibility of disposal of embryos to research with them, with the purpose of going further in the knowledge of the biological processes related to the beginning of life, fertility and the human genome. Accordingly with art. 18:

> " *In vitro* embryo experimentation. 1. Where the law allows research on embryos *in vitro*, it shall ensure adequate protection of the embryo. 2. The creation of human embryos for research purposes is prohibited".

Given the importance of this Convention, as first European legal framework on human rights that can be affected by biomedical sciences, it is suitable to make a more detailed study of art. 18. In my opinion it is not here time to deal with whether this article is or not coherent; in other words, if it has some internal contradictions or not. Anyway, as it is known, this provision was a result to get a way of consensus among the concerned bodies of the Council of Europe, having as a main goal to pass the Convention as a whole.

The knowledge of the exact meaning and extent of this precept requires a detailed, but complex analysis. To this respect we should take into account that the *Explanatory Report* of the Convention makes a brief commentary of this article, one of the shortest of all the Explanatory Report (margin numbers 115 and 116) and, therefore, it does not provide any help or interpretative orientation.

3.2. The first paragraph of art. 18 establishes that the States taking part in the Convention could authorise through a law (that is to say, it is a legal reservation: it could not be possible to authorise it as a normative instrument of minor range) experimentations with human embryos, this is, that the own decision is of the States, that may authorise or forbid such activity; when a State assumes a favourable position for experimentation, it is only imposed the obligation that law (this is again a legal reservation) have to guarantee an adequate protection of the embryo. Putting it in other words, law should include some type of guarantee that will entail an adequate protection. It has an extraordinary difficulty to establish how these guarantees should be, since the use of an embryo for research usually does not give place to its destiny to the human reproduction, unless this research will be in the direct profit of an own embryo. Therefore, it is needed a constellation of non-direct guarantees to protect embryos, but it is not necessary for an embryo concretely.

In the Draft of the Convention it was only established as a limit, consisting of that the embryo should not be developed further than fourteen days since the fertilisation, which was one of the possible guarantee ways. Once a different version has been finally approved, it can be said that it reaches both more and less limitations than in the initial version: the current text could be referred to other supplementary guarantees in addition to the ones that had been mentioned former (a limit of days for developing embryos); but also article 18.1 can be interpreted in a way that inside these guarantees it is not compulsory that research has to be limited to a certain maximum period, of fourteen days or otherwise (but with no doubt it is a clear guarantee and in my view it should be gathered in the laws on this matter). Other guarantees that the national legislation could include are, as an example, that research should be limited to very relevant scientific purposes; that the number of embryos

should be limited just to the necessary; that previous studies in laboratories and with animals should be done; that the used embryos for research should not be able for human reproduction; that the proposed research will be passed, supervised and controlled by an independent interdisciplinary committee, etc.

3.3. On the other side, the second paragraph of art. 18 establishes the prohibition that *in vitro* embryos are created with the purpose of experimenting with them, and besides this position is stronger than paragraph one about the suitable guarantees, it should have to be discussed by the international community, as a great number of researches may not agree with it, because they see it a curb to their necessities for research.

Anyway, from this paragraph 2, we should not deduce the absolute prohibition of embryo experimentation, as in this case paragraph 1 should not have any sense. To sum it up, we can deduce –we need to do a joint analysis of paragraphs 1 and 2 of art. 18- that the embryos which according the Convention could be used for experimentation, will be those that, initially created with reproductive purpose according to the legal framework of each national legislation, will not finally be used for this purpose, whatever the reason; that is to say, the surplus or supernumerary embryos from assisted reproduction techniques are the only outside the prohibition.

3.4. In any case, the prohibition only refers to the creation of embryos for experimentation purposes, but it is not when for other different purposes than reproductive, as it could be the therapeutic purposes for direct benefit of persons, using for that embryo material (stem cells). Therefore, this interpretative proposal, that could have great importance in the future, is that the Convention does not forbid in art. 18.2 the creation of embryos with a direct and immediate purpose of improving health or saving a person's life, as it is a radical different activity from experimentation. Accordingly this interpretation, we could understand that the European Convention has put the interest of embryo before collective interests (referred to the promotion of certain sectors in research), but that has put it -the human embryo- behind a concrete person's health and life (art. 2 of the Convention: "primacy of the human being")[33].

It is probably that this was not the aim of the authors of the Convention, and it is also true that the Convention is not clearly positioned on this important matter: neither in favour nor against such possibility (we can realize it, as in the date of approval of the Convention did not exist such important scientific developments). But it is not less true that, according to the usual interpretation techniques of lawyers, an objective analysis of the legal text allows to arrive to this conclusion, without forcing its literal meaning. On the other hand, this conclusion does not seem incongruous with the Convention as a whole, as it can be deduced from it-as well as from the human cloning Protocol of 1998- a wide range of axiological principles surrounding the *in vitro* human embryo, that constitutes the origin of its legal statute, pending of development by means of the corresponding Protocol. Going from a restrictive level to the most permissive step, here there are these principles, reported as some value steps:

i) The creation of *in vitro* human clone embryos for reproductive purposes is absolutely prohibited (art. 1 of the Protocol).

ii) The creation of human embryos for experimentation purposes is prohibited (art. 18.2).

[33] According to art. 2 of the Convention: "The interests and welfare of the human being shall prevail over the sole interest of society or science".

iii) It is necessarily deduced from the Convention, although it is not mentioned explicitly, that the creation of *in vitro* human embryos for industrial or commercial purposes is also prohibited (arts. 18.2 and 21).

iv) It is allowed that the States could authorise the use embryos for research, provided that they have not been concretely created for that purpose and that national law give guarantees for an adequate protection of embryo (art. 18.1).

v) It is necessarily deduced that, in view of the current technical means for human assisted reproduction, national legislations could count with the possibility of the production of supernumerary embryos as unexpected effect, that is to say, that they cannot be destined to their initial proposal of human reproduction (art. 18.1)

vi) Of the previous conclusion, it can be deduced that in view of the current technical means for human assisted reproduction, legislations of States could allow that more embryos than needed for an only transfer to a woman could be created with reproductive purposes, as well as the ones that have not been used in the first attempt will be cryopreserved for afterwards reproductive needs (successive repetitions of the attempt of pregnancy of the woman, if there have been previous failures) (art. 18.1).

vii) It can be accepted, as it is not explicitly prohibited, the creation of human embryos with therapeutic direct purposes for persons (art. 18.2).

viii) It can be accepted, as it is not explicitly prohibited, the use of supernumerary or surplus human embryos use with direct therapeutic purposes for persons (art. 18.1)

ix) The creation of human embryos for reproductive purposes by means of assisted human reproduction techniques besides the use of cloning is allowed (art. 18.1 and art. 1 of the Protocol). This could be also considered as having a therapeutic aim, to the extent it gives a solution for infertile couples.

3.5. The future Protocol on the legal statute of human embryo should bear in mind this axiological framework established both by the Convention and the Protocol on reproductive cloning, above all with the purpose of being more explicit in relation to some of the former conclusions. Nothing prevents that this Protocol may be either more restrictive or more permissive in relation with the interpretative conclusions that I have just proposed, provided that, in both cases, it is not clearly against the explicit text of art. 18 of the Convention, notwithstanding the established legal procedures previewed for its amendment (art. 32).

Therefore, there still exist the doubts about which could be, according the Convention, the suitable framework of guarantees for the embryo that is going under experimentation, and if the prohibition of creating human embryos for experimentation also reaches their creation with therapeutic purposes. We hope that the Protocol to the Convention related to the human embryo and foetus protection, on which the experts of the Council of Europe are working nowadays, cope now in a satisfactorily way these needs.

3. Current legal valuation: the need for a minimal harmonisation

1. As we have shown before, the matter of creation and use of human embryo with experimental or therapeutical purposes is far from being well legally defined, at least looking at the communitarian or international legislation and other state legal instruments, where we can see a great difference in quality of criteria.

Such a situation advises to be extremely cautious in relation with any normative decision concerning the *in vitro* embryo.

2. The different normative criteria that can be identified in Comparative and International Laws on the legal statute of the human embryo and foetus are a result of the ethical and social pluralism existing in the European countries. This pluralism is such a relevant value to be respected. As it has been stated by the European Group on Ethics in its conclusions, "respect for different philosophical, moral or legal approaches and for diverse cultures is implicit in the *ethical dimension of building a democratic European society*"[34].

This pluralism finds as an exception the human cloning with reproductive purposes, as well as the human embryo use with industrial or commercial purposes: both of them have deserved the general condemnation and prohibition.

However, it is also likely true that very important economic interests are involved in embryo research (including in that the trade with embryos or ES cell lines, and the aim of patenting them)[35], and it is sure that they are playing a relevant role for political and legislative decisions in some states. It should be an ingenuous approach not considering this so relevant matter, which the most times is hidden behind the ethical controversies.

3. At the moment, given the experimental character that these type of activities have currently and as long as the facts and ethical aspects concerned will not be better defined, it seems more recommended to follow the research in the second via (adult's, umbilical cord, amniotic liquid and foetuses' stem cells) than in the first one (to create embryos, clones or not), without prejudice of valuating the convenience of the authorisation of the recourse to supernumerary embryos stemming of assisted reproductive techniques, provided that previously the possibilities of their destiny for human reproduction in the couple from where they come or donating them to other couples, are tried unsuccessfully.

If in the future it would be possible to consolidate a therapeutic really effective line, and besides it can be proved that the only viable in the one that needs a forming of human embryos, whatever the used technique, we will be in front of an interests collision. Law now could provide the needed ways to give the right answer, by means of weighing up all the interests involved in the fact situation, and without any doubt sometimes could be solved in favour of the life or health of the ill patient, facing the *in vitro* embryo. Human embryo, if usually legally protected by means of laws that have taken care of these matters, also used to be protected in a minor way than other phases of prenatal life; that is to say, current penalties established for offences against the protection of embryo are less important than penalties established for implanted embryos and foetuses as well as for born people. Besides, usually, there are more exceptions to the protection of the *in vitro* embryo that to other kinds of further developed prenatal life.

4. According to what I have stated, we should insist on the need that also in the European level a suitable legal statute of the preimplantatory embryo should be created (*in vitro* and *in uterus*), in order to finish with the current misunderstanding and differences, in spite of the big difficulties that to achieve this success could present currently.

Taking into account that the European Union has no legislative competence to regulate directly research involving human embryos or parts thereof[36], the appropriate way to do this

[34] European Group on Ethics, *Opinion No 15 on Ethical Aspects of Human Stem Cell Research and Use*, cit., opinion 2.3.
[35] See Andrew POLLACK, *The promise in Selling Stem Cells*, in "The New York Times", August 26, 2001.
[36] In this presentation I don't intend to deal with an important discussion: whether ES cells are or not to be considered as a medicinal product or a medical device, and consequently to be regulated as these are. However my opinion is against this

is the Council of Europe and its legal instruments, as it is the Convention on Human Rights and Biomedicine.

Meaning while that very representative European States that still have not subscribed and/or ratified this Convention should look for some ways to do it as a first step for legal harmonisation, as by means of making a reservation in respect of any particular provision of the Convention to the extent that any law then in force in its territory is not in conformity with the provision (i e, to art. 18.2 in the case of United Kingdom in relation to the Act 1990), according to art. 36[37]; or maintaining a broader protection at the national law (i e, Germany, as it is the case by its current legal framework for human embryo), by the way of art. 27[38].

Anyway, may I wonder also whether it should be really advisable to try for a further step, looking for a common legal framework for Europe, avoiding the former so extensive different legal solutions, and whether we need to establish both different approaches for research and for therapeutic purposes involving human embryos. My personal view is just affirmative, both for economical and legal grounds: it is needed that all involved researchers and enterprises have a real equality of legal means to guarantee a truly competitivity among all of them at the European level. For research should be enough permitting the use of surplus embryos, and for therapeutic purposes the -use and- creation of somatic embryos from the patient might be permitted, in both cases when justified[39]. Notwithstanding, I understand that at present it seems to be an uncomfortable and unattainable task in short-term.

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focus, as art. 18 of EC on Human Rights and Biomedicine is an evidence for the need of a different approach. However, see a contrary criterion on the subject, Phil BROWN et alt., *Human cell- and tissue- based products: Progress, promise and regulatory issues*, in "Journal of Commercial Biotechnology", vol. 7, 4, pp. 287-298.

[37] For some comments to art. 36 of the Convention see Herman NYS, *La Convención Europea de Bioética. Objetivos, principios rectores y posibles limitaciones*, in "Revista de Derecho y Genoma Humano / Law and the Human Genome Review", No 12, 2000, pp. 67-87 (81).

[38] Art. 27 of the Convention stipulates: "None of the provisions of this Convention shall be interpreted as limiting or otherwise affecting the possibility for a Party to grant a wider measure of protection with regard to the application of biology and medicine than is stipulated in this Convention".

[39] This approach seems to be more limited in comparison with the Beyleveld/Pattinson proposal. In their view "harmonisation for permission seems to be well-nigh inevitable in the medium to long-term". See BEYLEVELD and PATTINSON, *Embryo Research in the UK: Is Harmonisation in the EU Needed or Possible?*, cit., p. 72. But it is also more extensive than the arguments against the use of human embryos for any purpose defended by Bertrand MATHIEU, *Les droits fondamentaux: les contraintes (?) du droit international et du droit constitutionnel*, in "Revue Générale de Droit Médical. Numéro Spécial: La recherche sur l'embryon: qualifications et enjeux", 2000, pp. 228 f.

Annex 5 : Opinion of the EGE concerning ethical aspects of human stem cell research and use

Annex 6 : Opinions from National Ethics Committees or similar bodies, public debate and national legislation in relation to human embryonic stem cell research and use – an overview[40]

Country	Has National Committee or similar body provided an opinion on human embryonic stem cells research and use ?	Will (or has) a public debate take(n) place?	What is the current legal/regulatory framework for human embryonic stem cells research and use[41]	Is any new legal/regulatory framework for human embryonic stem cells research and use in preparation under discussion?
Austria	No	No	The Austrian Reproductive Medicine Act states, that cells capable to development may only be used for medical assisted reproduction	In the course of the planned amendment of the Austrian Act for Reproductive Medicine (FmedG) the regulation of human embryonic stem cells research is currently under discussion
Belgium	No	No	No specific legislation related to research on human embryos	A government bill to regulate research on embryos and protection of embryos in vitro is currently being debated.
Denmark	Yes, the Danish Ethics Council	Yes	The question of Research on human stem cells/human embryos is regulated by par. 25-28 in the Act on Medically Assisted Reproduction : Biomedical research on fertilized ova and stem cells intended for reproduction can only be undertaken in the following cases : if the aim is to improve techniques for in-vitro fertilization in order to induce pregnancy and if the aim is to improve techniques of preimplantation diagnosis.	The Danish Minister for Health is preparing a revision of the legislation on human procreation within the next years.

[40] The information set out in the table has been collected by the European Commission, DG Research, Directorate E for Life Sciences. National Ethics Committees or similar bodies in the EU Member States, other European countries as well as Israel have been contacted during the period from March till September 2001. The complete survey which includes more detailed information is available from Dr. Line Matthiessen (email secretary: stephanie.caro@cec.eu.int).

[41] At national level, embryonic stem cell research and use is in most cases not regulated as such, therefore reference is often given to the general legislation on embryo research.

Country	Has National Committee or similar body provided an opinion on human embryonic stem cells research and use ?	Will (or has) a public debate take(n) place?	What is the current legal/regulatory framework for human embryonic stem cells research and use	Is any new legal/regulatory framework for human embryonic stem cells research and use in preparation under discussion?
Finland	No	Yes, probably	The Act on Medical Research (No. 488/1999) covers the preconditions and use of human embryos up to 14 days. No specific legislation on stem cell research.	The legislation on infertility treatments is under final preparatory stage and will give regulations also on ovocyte donations.
France	Yes ; Comité Consultatif National d'Ethique	Yes	Human embryo research is prohibited by law in 1994.	Yes
Germany	Yes, the Deutsche Forschungsgemeinschaft	Yes	Prohibited by the Embryo Protection Law	
Greece	No	No	The only legal framework operating in Greece is the Convention on Human Rights and Biomedicine and the additional protocol on the prohibition of cloning human beings.	No
Ireland	The Commission on Assisted Human Reproduction is currently considering the legal, ethical, medical and social issues in assisted reproduction and is expected to consider the issue of stem cell use in its advice to the Department of Health in 2002.	No	The provisions of the Irish constitution protect the right to life of the unborn but it is not clear whether this applies from fertilisation or implantation.	No

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Italy	Yes ; the Italian National Bioethics Committee	The public has been informed by the media. Nevertheless, this issue has been discussed in many conferences, and also in some meetings with students.	No legislation / regulation.	Law on in vitro fertilization under preparation.
Luxembourg	Not directly	Not directly	No legislation / regulation	No
Netherlands	Yes, the Health Council	In relation to discussion on human cloning	No legislation / regulation	The Bill on the handling of Human Gametes and Embryos was presented to Parliament in September 2000 and accepted by the 'lower house' (Tweede Kamer) in October 2001. The Bill is now on the agenda of the senate (Eerste Kamer), to be discussed there in the late winter or early spring of 2002. The envisaged legislation will also govern research involving human ES cells. The Bill contains provisions for the donation of embryos for research, including embryonic stem cell research..

Country	Has National Committee or similar body provided an opinion on human embryonic stem cells research and use ?	Will (or has) a public debate take(n) place?	What is the current legal/regulatory framework for human embryonic stem cells research and use	Is any new legal/regulatory framework for human embryonic stem cells research and use in preparation under discussion?
Portugal	No	No	No legislation / regulation	No
Spain	No	No	This matter is regulated by the Assisted Reproduction Techniques Act of 1988[1]. This Law only allows the following activities concerning research with human embryos: 1. Cryopreservation of embryos is permitted by Law, which means that the possibility of having supernumerary embryos from assisted reproduction techniques is not excluded. 2. Research or experimentation on *in vitro* human biologically non-viable embryos, under certain conditions (art. 15.3). 3. When they are aborted preimplantatory embryos, they are considered dead or non-viable, and can be used for several purposes, above all research (art. 17). 4. Finally, in the case of viable *in vitro* embryos, it is allowed research if applicable to diagnosis with therapeutic or preventive purposes (in other words: for the benefit of the embryo), and if no modification of genetic non-pathologic heritage of embryo is ensured (art. 15.2)[2]	No
Sweden	Yes, the Swedish Medical Research Council	Yes	On in vitro fertilization (1988) and Law regarding research on treatment using fertilized human ova (1991). Embryo research is legally permitted since 1991 until day 14 after which the embryo must be destroyed. The current guideline proposals do not permit somatic cell nuclear transfer or creation of embryos solely for research purposes and there is no legislation on these issues. Selling of human biological material is forbidden is Sweden.	

[1] Law 35/1988, of 22 November.

[2] See Carlos M. ROMEO-CASABONA, *El Derecho y la Bioética ante los limites de la vida humana,* Ed. CERA, Madrid, 1994, pp. 393 f.

Country	Has National Committee or similar body provided an opinion on human embryonic stem cells research and use ?	Will (or has) a public debate take(n) place?	What is the current legal/regulatory framework for human embryonic stem cells research and use	Is any new legal/regulatory framework for human embryonic stem cells research and use in preparation under discussion?
United Kingdom	Yes, the Nuffield Council on Bioethics	Yes	Human Fertilization and Embryology Act, 1990 The Human Fertilization and Embryology (Research purposes) Regulations, 2001. Embryo research is permitted under the HFEA Act for any of five specified purposes, briefly: - To promote advances in the treatment of infertility - To increase knowledge about the causes of congenital disease - To increase knowledge about the causes of miscarriage - To develop more effective contraceptive techniques - To develop methods for detecting gene or chromosome abnormalities in pre-implantation embryos. In January 2001, Regulations were made extending the purposes for which embryo research could be licensed. The further purposes are: - To increase knowledge about the development of embryos - Increasing knowledge about serious disease - To enable such knowledge to be applied in developing treatments for serious disease.	
Croatia	No	Not yet	No legislation / regulation	No
Estonia	No	No	No legislation / regulation	No
Hungary	No	No	The human embryonic stem cell research and use is regulated by law and three decrees.	A new decree dealing with biomedical research is under preparation.

Country	Has National Committee or similar body provided an opinion on human embryonic stem cells research and use ?	Will (or has) a public debate take(n) place?	What is the current legal/regulatory framework for human embryonic stem cells research and use	Is any new legal/regulatory framework for human embryonic stem cells research and use in preparation under discussion?
Iceland	No	No	The only provisions relevant for embryonic stem cells research are provisions in the Act on Artificial Fertilization Act No. 55/1996, where Research on Embryos is dealt with in Art. 11 and 12. Art. 11 : all research, experiments and operations on embryos is prohibited Nevertheless, it is permitted to carry out research on embryos : a) if it is part of an in vitro fertilisation treatment, b) if the intention is to diagnose hereditary diseases in the embryos themselves, c) if the purpose is to advance the treatment of infertility, or d) if the purpose is to improve understanding of the causes of congenital diseases and miscarriages.	No
Israel	Yes, the Israel Academy of Sciences and Humanities	No	Public Health (extra-Corporal Fertilization) Regulation 1987 ban the creation of embryos for purposes of research and therapy except for reproductive purposes.	Not yet
Latvia	Yes, theCentral Medical Ethics Committee	Few public debate has been induced by draft Act on Human Reproductive and Sexual Health. There were a big difference in opinion between public and religion.	Convention on Human Rights and Biomedicine. Draft Act on Human Reproductive and Sexual Health Regulation of Ministry of Welfare of Latvia on human medical assisted reproduction No. 173, June 10, 1999. There is not any regulation directly on human embryonic stem cells research and use.	No
Lithuania	No	Yes	Lithuanian Law on Biomedical Research allows only observational studies of human embryo. All other research with human embryo are forbidden.	
Switzerland	Yes, the Central Ethics Committee of the Swiss Academy of Medical Science	Yes	Since January 2001, a new law of reproductive medicine is put into force. The separation of cells from human embryos for research purpose is forbidden.	Yes