Does the French Bioethics Law create a 'moral exception' to the use of human cells for health? A legal and organisational issue

¿Establece la ley francesa de bioética una "excepción moral" para el uso de células humanas en la salud? Un problema jurídico y organizativo

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ABSTRACT: This article focuses on the legal and organisational regulation of human cells in the United Kingdom and France. French Bioethics Law regulates human cells for health according to European Union law where it is enforceable. But products unregulated by EU law and based on human cells are never considered as medicinal products, given the strict implementation of the principle of "non-patrimonialité" of the human body and its elements. By comparison, in the UK such products can be qualified as medicinal products. Moreover, the setting up of the UK stem cell bank gives rise to the development of policies which expand the stem cell as a legal object. The paper discusses how these societies' ethical and legal commitments underlie organisational practices in order to analyse the relationship between the existence (or not) of a national stem cell bank and the broader regulation of human cells.

KEYWORDS: Human cells, national stem cell bank, principle of non-commercialisation, France, United Kingdom, European Union, social arrangements, bioethics

RESUMEN: Este artículo se centra en la regulación legal y organizativa sobre células humanas en el Reino Unido y Francia. La ley de bioética francesa regula las células humanas para la salud de acuerdo con la legislación de la Unión Europea, donde ésta tiene vigencia. Sin embargo, los productos no regulados por la legislación de la UE que hacen referencia a las células humanas no son considerados como medicamentos sujetos a la estricta aplicación del principio de "no patrimonialidad" del cuerpo humano y sus elementos. En comparación, estos productos en el Reino Unido pueden ser calificados como productos medicinales. Por otra parte, la creación del banco de células madre en el Reino Unido da lugar al desarrollo de políticas de elaboración que se expande a las células madre en el campo de los objetos jurídicos. Este artículo muestra cómo los compromisos éticos y legales que estas sociedades han adoptado subyacen a las prácticas organizativas de estos países. Su propósito es analizar la relación entre la existencia (o no) de un banco nacional de células madre y la regulación más amplia del uso de células humanas.

PALABRAS-CLAVE: Células humanas, banco nacional de células madre, principio de no comercialización, Francia, Reino Unido, Unión Europea, acuerdos sociales, bioética

0. Introduction

Human cells are now recognized for their potential in therapy. Although this is true for many years for blood transfusion, their potential uses to treat patients become wider as development of sciences and technologies continuously open new perspectives (Le Douarin, 2000;

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Nowotny and Testa, 2011). They give rise to a real excitement because they could lead to revolutionary treatments for untreated diseases. Whereas they are broadly publicised in the media, sometimes confusedly, we have to be cautious. Indeed, human cells are various and they are at different stages for human application. In this paper, we will focus on human stem cells[1] as they are seen to have broader therapeutic potential. Even though there are current therapeutic applications using adult stem cells and fetal stem cells, embryonic stem cells are rather at the research stage. Nevertheless, high therapeutic expectations are attached to them. Research on human embryonic stem cells (here after "hESC") obtained by nuclear transfer seem to have been almost totally abandoned in the countries where this technique is authorized, such as in Spain.[2] All the more since induced pluripotent stem cells (hereafter "IPS") have been discovered (Takahashi and al, 2007). However, therapeutic applications using IPS appear far away. Here also we have to be cautious as progress of science is unforeseeable as it appears now that researchers need not obligatorily attain an undifferentiated stage of cell structures to initiate any differentiation pathway, key to 'pluripotency'. Indeed, it has been recently shown that activation of hepatocyte differentiation can induce hepatocyte-specific properties in different cell types (Sekiya and Suzuki, 2011). But at the same time, some uncertainties increase notably regarding the stability of cells. So, there is a shift from a regime of truth to a regime of hope (Brown, 2007). Thus, it makes sense, also given the high degree of public and political attention that has been given to stem cells, and especially human embryonic stem cells, that scientific and regulatory activity in this particular field may have a 'spill over' effect on cell-based therapy more generally.

In order to investigate this proposal, therefore, this paper proposes a comparison between French and British regulation of stem cells, taking into account the broader cell therapy context. These two countries have a very different approach regarding the medical use of human cells and stem cells lines in particular. However, they cannot be considered totally independently as both are Member States of the European Union. Thus various trends, including legal and regulatory trends, at different levels, have to be taken into account. Two distinct legislations have been adopted. They are related either to human cells as *elements of the human body* according to the EU competency in public health or to *medicinal products* based on human cells according to its economic competency.

Originally only economic, the European Union can now also legally act in the field of public health.[3] As we will see below, the European Union

ISSN: 1989-7022 DILEMATA, año 3 (2011), nº 7, 17-37

has adopted binding rules for human cells used in therapy, which are enforceable in France and the United Kingdom. Two distinctive legislations have been adopted in the respective national policies.

On the one hand, France is known to be "very protective". Indeed, French law provides a high respect of the human person and its body through its traditions, which embrace a human rights approach. France has had a Bioethics Law since 1994 which regulates the therapeutic use of human cells. This law has just been revised but the revision does not provide fundamental change concerning the regulation of human cells.[4] Debates during the revision of this law focused on research aspects on human cells, and particularly on hESC, and not on therapeutic applications.[5] On the other hand, the United Kingdom is known to be "liberal and highly regulated", but there is no specific bioethics law in the United Kingdom. Two main acts cover human cells for therapy: the 2004 Human Tissue Act and the 1968 Medicine Act (as amended).

Given the national legal and institutional differences and over-arching EU legal framework that we will describe, the key question addressed in this paper is: Does the French Bioethics Law create a "moral exception" to the use of human cells for health? In other words, we would like to show whether the French regulation of human cells for health is specific and distinctive on the basis of its strong attachment to principles of fundamental rights, especially the respect of the human person. Does this attachment mainly arise from the Bioethics Law framing the regulation of human cells for health and limiting their prospective uses? The issue appears very important as one can wonder if France will stay in the background internationally regarding therapeutic uses of human cells due to its specific regulation, whereas the EU –and more specifically the UK- already made it a priority through supporting regulations and commitments. Indeed, the EU is enhancing access to innovative therapies including medicinal products based on human cells[6] and the UK is developing an integrated national strategy for regenerative medicine where stem cells are already emphasised (Department for Business, Innovation & Skills, Office for Life Sciences, Department of Health, 2011).

This question will be analysed from two points of view which are connected together: a legal approach and an organizational one. On the one side, we will demonstrate that the legal regulation of human cells in France is particular and distinct from that of the UK despite the harmonisation provided by the European Union and its national implementations. On the other side, from an organizational point of view and by a comparison between the UK, where a national stem cells bank has been set up, and France, where there is no national bank at the mo-

DILEMATA, año 3 (2011), nº 7, 17-37 ISSN: 1989-7022

ment, we will analyse the relationship between the existence (or absence) of a national stem cell bank and the nature of the regulation of human cells: How different legal systems framed the possibilities for the establishment of a national stem cell bank? Or, in other words, can we deduce that the absence of such a scientific institution is associated with significant national differences in human cell therapy regulation?

1. A legal issue: the particularity of French law

Human cells in the legal frame are either considered as elements of the human body or as products for health. Whereas it corresponds to two different sets of legislations in the EU and in the UK, the distinction is made within one law in France: the Bioethics Law.

1.1. Human cells as elements of the human body

EU law, French law and English law regulate human cells as elements of the human body. The most problematic issue from a perspective of development of medical treatments is related to access to cells which are parts or elements of the human body. These legislations are framed through the protection of persons from whom the cells are removed. But different aspects are highlighted according to each law.

EU law points out the quality and safety requirements of cells used for therapy. The Directive 2004/23/EC of 31 March 2004, often called the "mother directive" or the "Tissues and Cells directive", provides the framework legislation.[7] Two supplementary technical directives provide detailed requirements regarding the procurement of human tissues and cells, the selection criteria and the laboratory tests for donors, the tissue establishments and the direct distribution to the recipient as well as the traceability, the notification of serious adverse reactions and events and the coding, processing, preservation, storage and distribution of human tissues and cells.[8] The legal basis for the directive on tissues and cells was ex-article 152 of the European Community Treaty (new article 168) on the protection of human health.[9] That is why, according to the objective of public health protection, the minimum quality and safety standards for cells are the same in all of the EU member States. Such requirements cover also specific types of human tissues or cells, or cells from any specified source, including the most sensitive particular human cells, i.e. germ cells and embryonic stem cells.[10] Indeed, Member States are free to authorise or prohibit the uses of hESC but, if they are authorised, they must respect the provisions of the directive on tissues and cells.[11] This directive also provides ethical and legal principles which aim to protect the human person: voluntary and unpaid do-

ISSN: 1989-7022 DILEMATA, año 3 (2011), nº 7, 17-37

nations,[12] consent,[13] non-profit basis of procurement of tissues and cells,[14] data protection and confidentiality.[15]

France

In France, the Bioethics Law regulates the human body and its elements through the implementation of fundamental rights around the core principle of the respect of the human body. Since 1994, this principle is declined in various principles of application such as free and anonymous donation, informed consent, and non-ownership,.[16] French law in particular strongly implements the principle of *non–patrimonialité* of the human body and its elements which is integrated within the civil code. The latter is the general legal instrument which regulates the set of person's rights. As such, this principle has a general impact in law. It means that the human body and its elements cannot be the object of a financial agreement[17] and that any agreement which gives them a financial value is void.[18i] This principle is very close to the principle of *non-commercialisation* but we could say that it is even broader and includes it. So in this paper we consider that it corresponds better to the English principle of "non-commodification" which is broader, but not included in a law yet. Before the *non-patrimonialité* principle became a general legal principle in 1994: the ethical principle of *non-commercialisation* was already clearly established for ten years in France. Indeed, it was asserted from 1984 within the first opinion of the French National Ethics Committee (French National Ethics Committee, 1984) and then regularly re-asserted until the committee dedicated an entire report to this principle, in 1990: "Neither the human body nor any parts of it can be sold or bought", "any elements detached from the body can be assimilated to a good, even through a legal tool such as a patent" (French National Ethics Committee, 1990). The *(non-) commercialisation* is also considered for blood transfusion and stem cells directly in legal measures of 1991(French National Ethics Committee, 1991a) and 2006 (French National Ethics Committee, 2006). The affirmation of this principle has strong consequences on the vision of French society regarding the uses of cells in research (specifically on hESC) as well as on researchers' practices.[19] As an example, hESC research is still forbidden by principle[20] according to the new French Bioethics Law while various agencies have pushed to move to a regime of authorisation.

United Kingdom

In the United Kingdom, the 2004 Human Tissue Act regulates human cells as elements of the human body. Although it is not possible to say this legislation is based on fundamental rights compared to French law, it should be noticed that this Act is entirely framed around the princi-

DILEMATA, año 3 (2011), nº 7, 17-37 ISSN: 1989-7022

ple of informed consent, which aims to protect the person from whom the cells are removed. It would be wrong to think that the UK was late to regulate human cells compared to France, even though the previous 2004 legal framework was quite incomplete (McHale, 2010)[21]. Indeed, the Human Tissue Act 1961 already provided that any person had to express an explicit request (nowadays an informed consent) that his or her body or any specified part of it could be used for therapeutic purposes after death. Moreover, according to the Human Fertilisation and Embryology Act 1990, the use of gametes or embryos for infertility treatment or research was lawful if the necessary consents had been given as provided by Schedule 3 of the Act. At this time, the therapeutic use and removal of cells which did not appear within the Statutes, such as the use of cells removed from the living, was a matter of common law. In 1995, the Nuffield Council on Bioethics issued an opinion on "Human Tissue: Ethical and Legal issues" where human tissue was defined broadly as it encompassed "sub-cellular structures, cells and their products, tissues and organs". In this Opinion, the Council considered that the public interest criterion would "most likely" be the one that a court would "employ if the legality of any particular use of tissue were challenged". Since 1961, the principle of informed consent is a fundamental one as far as removal and use of human cells or tissues are concerned. Thus, in the UK, we can note that 'public interest' is likely to be an over-riding criterion in matters of regulation of therapeutic innovations based on viable human material, and we can interpret this as likely to make reference to matters of future health of the population.

1.2. Human cells as products for health

In the EU, health products which are based on human cells can be regulated either by EU law or by national laws according to the legal qualification of the final "product" which notably depends on its preparation process.

Health products based on human cells and regulated by EU law are now deemed to be somatic cell therapy medicinal products.[22] As such, they are one kind of 'advanced therapy' medicinal products, a legal category created in 2003[23] and clarified in 2007 through the adoption of the regulation (EC) N°1394/2007 on advanced therapy medicinal products (ATMP) (Hereafter the regulation on ATMP).[24] This regulation is a *lex specialis* and so sets up a legal framework which is stricter than the one enforceable for other common medicinal products. To be covered by this regulation a product based on human cells has to fulfil two cumulative conditions (Mahalatchimy, 2011). On the one hand, it has to correspond to the legal definition of a somatic cell therapy medicinal

ISSN: 1989-7022 DILEMATA, año 3 (2011), nº 7, 17-37

products which "contains or consists of cells or tissues that have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, or of cells or tissues that are not intended to be used for the same essential function (s) in the recipient and the donor; [and] is presented as having properties for, or is used in or administered to human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues".[25]

On the other hand, the medicinal product shall be "intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process".[26] However, this regulation also provides a hospital exemption for ATMP which are "prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient".[27]

As such, they are not covered by the regulation on ATMP and have to comply with national rules.

In general, apart from those medicinal products based on human cells which are regulated by EU law, other human cells-based health products which are not covered or are excluded from the regulation on ATMP are regulated by national laws. While both the UK and France provide a legal regime for health products based on human cells which are not regulated by EU law, France refuses to qualify them as medicinal products, unlike the UK.

In France, health products based on human body elements, such as genes, cells and tissues prepared in advance to one or several patients on medical prescription, are called "preparations". As there is no industrial process, they are not submitted to the EU legislation on ATMP. The marketing authorization is delivered by the French Agency for the Safety of Health Products (AFSSAPS) for a specific therapeutic use.[28] Whereas gene therapy preparations or xenogenic cell therapy preparations are qualified as "medicinal products", human cell therapy preparations are not. That is why, the latter fall under the legal regulations governing human cells and tissues.[29] When health products are legally qualified as medicinal products, it means that they are goods submitted to market rules, such as the principle of free movement of goods coming from EU law. But we can see that France –in accordance with its strong attachment to the principle of *non-patrimonialité*-refuses such

DILEMATA, año 3 (2011), nº 7, 17-37 ISSN: 1989-7022

legal qualification of medicinal products for health products –unregulated by EU law- based on human cells, . Human embryonic stem cells are ethically more problematic as they come from a human embryo which has been qualified by the French National Ethics Committee as a potential human person (French National Ethics Committee, 1984, 1991b). Moreover, access to hESC implied the destruction of the embryo. While a new way to obtain hESC may be open through IPS, at the moment, it is scientifically controversial to say that IPS are identical to hESC (Hewitt and al., 2011).

In the UK, it is commonly admitted that human body elements used for the development of therapeutic products should be obtained on a non-commercial basis (Nuffield Council on Bioethics, 1995). Although initially public discussion about the existential status of hESC was very controversial, provoking heated debate in both Houses of Parliament, the principle of non-commercialisation of the human body has not been deemed to be a general and fundamental guiding principle in the same way as it is in France. Even though the question of commodification of the human body parts has notably been enunciated by the Nuffield Council on Bioethics, such an issue has been considered indirectly through the question of the property of the human body and its elements (Nuffield Council on Bioethics, 2010; McHale, 2010, 1036; Dickenson, 2007). Indications on this issue are expected from a report with recommendations for policy from the Nuffield Council on Bioethics that will be published in autumn 2011.

1.3. Discussion

The social meaning of human cells *in situ* is assimilated in prevailing discourses of contemporary societies to belief in the integrity of the human body and even to the human person. As such, human cells could benefit from the rights which protect the person. But with the evolution of science, human cells have been isolated and became a scientific object that could be treated as a biological material totally detached from the body and, as a consequence, from the person. This autonomy of the cells from the human body has made possible and conceivable their potential uses in research and therapeutic practice. However, at this point, somatic cells should already be distinguished from embryonic cells.

On the one hand, somatic cells can be considered as parts, and going a step further as elements of the human body, according to criteria of detachment or distance from the body. This is translated as "removal of elements of the body" in law. A cell is more easily removed from the body than an organ or a limb without infringing the integrity of the human body. Moreover, the cell (as other elements or parts of the body)

ISSN: 1989-7022 DILEMATA, año 3 (2011), nº 7, 17-37

has an interest because it is linked to therapeutic promises. What researchers call 'stem cells' are even more interesting as they are associated to the idea of "regeneration". Thus, it is of legal and ethical significance to qualify human cells as human body *elements* because when they are autonomous from the human body, they can be used for therapy.

On the other hand, it is more complicated for embryonic cells because it is not the cell which is removed from the human body. First of all, the embryo has been dissociated from the body and from fertilisation with the development of techniques of medically assisted procreation. Then, the embryonic cell has been detached from the embryo. The consequence of this physical link between the embryonic cell and the embryo was their assimilation, their epistemic connection in people's minds. The notion of "potential human person" attributed to the embryo by the French Ethics Committee, the embryonic cell attachment to the embryo, the destruction of the embryo to access the embryonic cell and the potentiality of the embryonic cell (totipotent embryonic cell) to become a person if implanted in vivo, gave rise to the association between the person and the embryonic cell, confounding the latter with the embryo. But the appearance of supernumerary embryos (which can be destroyed under specific conditions) associated with the therapeutic promise of embryonic cells devoid of any parental project, and the distinction between different types of hESC (totipotent, pluripotent, multipotent and unipotent) have permitted a distinction between the cell and the embryo and consequently, between the cell and the person.

Once detached from the body, the cell remains a human body element, protected as such through informed consent, and free and anonymous donation principles. Its uses are restricted by the principle of *non-patrimonialité* and organised in accordance with the respect of fundamental rights in France, whereas in the UK, its uses are framed around the principle of informed consent.

But known or potential therapeutic promises have justified the modification of the cell. Where transformed or manufactured, it becomes a product for health, submitted to market rules. The existence of legislations at the European level as well as at the national levels is a proof that the cell can also legally be recognised as a product for health. In such a context, France has a distinctive legal and ethical approach as it refuses to qualify as medicinal products human cells-based products that it regulates. However, France faces a decline in the principle of "non-patrimonialité" given the challenge of implementation of EU law. Indeed, 'industrialised' somatic cell therapy medicinal products are qualified as medicinal products as ATMP,[30] undermining the French po-

DILEMATA, año 3 (2011), nº 7, 17-37 ISSN: 1989-7022

sition. Similarly, ATMP which are excluded from the scope of the regulation on ATMP under the hospital exemption are regulated by national laws. But their qualification as ATMP by EU law implies there are medicinal products in French law too whereas before the adoption of such regulation they were qualified as "human cell therapy preparation" and were not considered as medicinal products. Thus, in summary, the new category of ATMP under the hospital exemption reduces the extent and strength of the French legal category of human cell-based health products not considered as medicinal products.

As France has a particular, distinctive legal regime for human cells health products, we will analyse if and how this may be linked to the absence in France of a national stem cells bank. We undertake this analysis by comparing the French regulatory regime to that in the United Kingdom where a national stem cells bank has now been established for some years.

2. An organizational issue: the impact for the establishment of a national stem cells bank

The existence of a national stem cell bank for research purposes illustrates the importance given to such a field in a country by its government. Where stem cells research is favoured in public policy, new therapies based on stem cells are more likely to be developed. That is why the European Union is active in this domain, and the UK, which has a national stem cell bank since 2003, is recognised as a leading State in the EU in this area. Despite the fact that the UK stem cell bank has been for a long time far from establishing injectable products directly to patients, promoters of the bank plan larger and permanent facilities to store and distribute cell lines with good quality control. Clinical grade cell lines were therefore in the long term vision for the bank. Organizational contiguity between the banking-oriented research and clinical orientation naturalizes the shaping of collective expectations toward possible medical applications (Tournay et al, 2010). Like the promises formed around the cord blood banks, the UKSCB achieves a co-construction of a set of projections and a therapeutic chain of preparation of cell products including technical details (which have been strongly debated) (Martin and al, 2008). The United Kingdom Stem Cell Bank's architecture itself may be seen as having organizational effectiveness (Stephens and al, 2008a). It is notable that the UK stem cell bank recently accepted for banking the first *clinical grade* human embryonic stem cell lines in readiness for clinical trials (Department for Business, Innovation & Skills, Office for Life Sciences, Department of Health,

ISSN: 1989-7022 DILEMATA, año 3 (2011), nº 7, 17-37

2011), thus paving the way for a therapeutic treatment developed from a stem cell line, and possibly later development of a 'product'.

A national stem cell bank may "fill a regulatory gap" as it may lead to the development of practices which become *de facto* regulatory (e.g. safety standards) by developing principles for testing and data requirements which are then copied or translated between scientific institutions. In the case under consideration here, it may also come to be treated by interested actors as a 'model' for other cellular advanced therapies through various forms of linkage to the UK stem cell bank (Faulkner, 2008).

Unlike the UK, there is no national stem cell bank in France, although the setting-up of such a body has been discussed, mainly by researchers, as we will see below.

The aim here is to have a closer look at the legal and ethical commitments underlying scientific research and therapeutic producers' organisational practices and perspectives, and to examine the relationships between legal/ethical principles and the shaping of organisational forms if we focus our attention on controversies about potential models of French physical stem cell banks. The comparison with the UK legal frame can be taken as a good 'social laboratory' to develop a better understanding of the conditions which predispose toward emergence of a national stem cell bank, and to understand the consequences of the French 'moral exception' in the regulation of human cells for the setting-up of such bank.

2.1. A national stem cell bank in the United Kingdom

The UK stem cell bank (UKSCB) was established in January 2003 with a grant from the Medical Research Council and the Biotechnology and Biological Sciences Research Council.[31] It collects and provides human embryonic stem cell lines for research purposes around the world. The operation of the UKSCB expanded the stem cell as a regulatory object which was then regulated by the EU tissues and cells directive and the Human Tissue Act 2004. Indeed, its code of practice for the use of human stem cell lines (UKSCB, 2010), although non legally binding, is a major and necessary text framing the use of human stem cells. Moreover, the UKSCB developed good manufacturing practices which has been recognised by the scientific community of the field: the UKSCB "is an accredited Good Manufacturing Process (GMP) cell facility and their experience in this complex process has been invaluable to many in the stem cell community establishing GMP-level cell and tissue culture facilities" (Minger, 2006).

DILEMATA, año 3 (2011), nº 7, 17-37 ISSN: 1989-7022

The UK Government's role has also been significant in its promotion of human stem cell research and has enabled the setting-up of the bank. It encourages dialogue with the public on issues around stem cells, which generally supported the role of the UKSCB as a repository for stem cell lines for research and therapeutic use (Biotechnology and Biological Sciences Research Council and Medical Research Council in collaboration with the Sciencewise Expert Resource Centre, 2008). If the UK has managed to create a 'national' resource in such a highly sensitive field of bioscience, it implies a degree of public trust and consensus or network of trust[32] about the social legitimacy of the institution itself (i.e. the bank) and the legal and quasi-legal safeguards built into it. Thus we suggest that there might be a spillover effect for public confidence in cell-based therapeutic regulation more generally as the "stem cell dialogue" final report provides: "The governance of UK stem cells was often viewed as a success story by participants. Most strongly articulated by government stakeholders, who saw the UK as leading the world in this area, many viewed the supportive regulatory environment as a significant factor in contributing to favourable public opinion and assisting development of research. However, governance in this area is complex and often contested". (Biotechnology and Biological Sciences Research Council and Medical Research Council in collaboration with the Sciencewise Expert Resource Centre, 2008)

The UKSCB, therefore, although non-statutory, has been interpreted as having adopted a 'guardianship' role and as acting as an 'institution of regulation' (Stephens et al, 2008b). Of particular interest to this discussion is these authors' consideration of the question of 'How does the Bank relate to laboratories and other regulatory institutions both domestically and internationally?'. As these authors make clear, the UKSCB had become a key part of a network of relations between organisations donating stem cell lines, and part of the duties created for the Bank's Steering Committee, which deals with social, ethical and legal issues, is to check that the donation is lawful in the country of origin. The Committee may refuse an application if the credentials of the donor organisation cannot be established. Stephens *et al* also show how documentation, in the form of information forms between the contracting parties, play a part in the development of trust relations between the Bank and laboratories. The authors emphasize how the Bank's work is thus constitutive of 'social networks' in which trust between participants is a key feature in stabilising the social relations of scientific work. The UKSCB is both regulator and regulatee – it fits into a frequently-changing patchwork of both UK and EU laws, regulations and codes of practice, including the Human Tissue Act and the Human Fertilisation and Embryology Authority. Bank staff see themselves as

ISSN: 1989-7022 DILEMATA, año 3 (2011), nº 7, 17-37

developing a world-leading quality assurance system in their field, which can act as an example of good practice and model for cellular scientists and product developers more widely, thus they are involved in issues of 'social legitimacy and stabilized networks of accreditation' (op.cit.). Thus, the UKSCB becomes regarded as a 'model' as it is "internationally acknowledged as the leader in stem cell banking […]. It is a world recognised source of best practice and regulatory standards, as well as a provider of education and training for the community" (Department for Business, Innovation & Skills, Office for Life Sciences, Department of Health, 2011). We can note that the donating institutions and customer laboratories of the UKSCB may be involved in cell-based research and product development beyond the narrower case of stem cells per se, thus there is a likely spillover regulatory effect. Indeed it may make sense to think of a growing international 'hierarchy of regulatory credibility' in the cell research and therapy field broadly, in which human embryonic stem cell regulation is at, or near, the top.

2.2. The organisational consequence of a binding legal regime: Towards a national embryonic stem cell bank in France?

In France, in contrast to the UK, there is currently no national stem cell bank. During the last revision of the French Bioethics Law,[33] the parliamentary office for the evaluation of scientific and technological options (OPECST) proposed to create a national bank to centralize and distribute stem cells which would be an intermediary for national and international entities and simplify administrative processes (OPECST, 2010). However, no decision has been taken yet as there are divergences regarding the frame and the functions of a national stem cell bank. For instance, should the centralized UK model or the decentralized Spanish model be followed? Furthermore, French researchers disagree on the place where the cells have to be prepared. Should the bank only be an establishment of storage of cell lines or should it be an establishment to amplify and prepare the cells? (Tournay, 2008)

It appears that the first obstacle for a French national bank is not related to human cells but to hESC, which are the object of a lot of pressures from researchers. Research on the embryo and on embryonic stem cells is prohibited in France as a matter of principle, although since 2004 a special dispensation has been permitted. The "Agence de la Biomédecine", which ensures that each stage of the research conforms to legal and ethical regulations, can allow research on human embryos and embryonic stem cells where major medical (Conseil d'orientation de l'Agence de la biomédecine, 2008)[34] progresses may be possible in highly controlled conditions.

DILEMATA, año 3 (2011), nº 7, 17-37 ISSN: 1989-7022

However, as there is no physical bank in France where researchers can store their stem cell products, once they have received official authorisation, researchers work on supernumerary embryos donated to research or on embryonic stem cell lines derived/established and stored in foreign countries. France is characterized by a well-defined policy on human embryonic stem cells, while the potential model of embryonic stem cells' storage for scientific purposes is highly controversial.

A range of reflections on the possible setting-up of a bank has existed for many years between researchers who work on embryonic stem cells and members of the French Biomedicine Agency. But those reflections have to comply with specific rules that biologists who receive authorizations for working on hESC lines have to follow:

- Researchers have to insure traceability, safety and quality requirements of their embryonic products throughout the course of their research.

- They also have to comply with the research protocol in which the French Biomedicine Agency agreed first when the research team applied for authorisation. They cannot use hESC for other purposes than those originally planned and they cannot send them to other teams as – for example – to outsourcing laboratories that practice quality controls.

- Authorization of research is made for the using of one specific line. So, researchers cannot substitute to another line even if they consider that would be relevant for one moment of their research.

Moreover, where quality and safety of all human cells based therapy products fall under the remit of AFSSAPS (clinical trials, therapeutic uses), the French Biomedicine Agency is specifically in charge of the derogative authorisation under strict legal conditions of research on hESC. We propose to qualify the latter as "high-grade ethics 'products'" as they raise deep ethical controversies because of their strong epistemic connotation with the whole person. That is why they are submitted to a specific legal regime under the supervision of a specific Agency: the French Biomedicine Agency.

Thus, constraints on embryonic products are higher than those applied on classical 'cell therapy products', primarily consisting of differentiated adult cells.

Taking into account these requirements, or maybe to compensate them, the necessity of a physical bank located in France to centralize stem cell products has been acknowledged by researchers of the embryonic

ISSN: 1989-7022 DILEMATA, año 3 (2011), nº 7, 17-37

stem cells community and the French Biomedicine Agency. But the internal organization of this structure of storage remains highly controversial among the interested actors.

2.3. Models of hESC banks: A close link between legal framework and organisational practice

In France, researchers have a dual association to hESC due to the fact that the technological demarcation between embryonic and differentiated stem cells remains unclear. On the one hand, the aim is to try to maximize self-renewal and the maintenance of pluripotency of stem cells -i.e. an undifferentiated state- and, on the other hand, researchers want to lead their cell differentiation into a wide range of cell types. But, in any case, practitioners have great difficulties in strictly maintaining hESC in an undifferentiated state throughout the course of cell culture processes.

This embryonic cell material is grown according to the protocols acknowledged by the French Biomedicine Agency. The French agency needs to regulate a set of cell cultures which is more or less differentiated or, in other words, more or less embryonic. This practical fact is not without consequences in the regulation of these products because some research teams claim that these products are no longer "embryonic" cells. According to these claims, these products would have to stand outside the particular, distinctive regulation for hESC cells. According to some biologists, these products are closer to the legal frame of 'cell therapy' which regulates differentiated or adult stem cells (Tournay, 2008). This claim has concrete effects on the regulation of these products as we will see now.

The way that researchers conceptualise the stage of the demarcation between 'embryonic culture' and 'differentiated culture' has important consequences for how the organization of a potential national stem cell bank in France is conceived. Indeed, various rival models of banking have been promoted and challenged by researchers who work on hESC to define a legitimate public policy object in different ways.

On the one hand, researchers who have the tendency to semantically detach the growth of embryonic cell culture from the life of the human embryo, generally want to develop a 'bank of service'. On the other, researchers who, on an ethical level, assimilate the development of hESC most strongly to that of the human embryo, usually want to develop a simple platform of storage.

So, they face two rival models of banking. The first is strictly a model of biobanking activities characterized by the storage of cell line samples

DILEMATA, año 3 (2011), nº 7, 17-37 ISSN: 1989-7022

and the delivery of these samples to the requesting teams. This vision of bank aims at collecting reliable information from various places and mapping delivery of cell lines to national teams. This model has the support of persons who consider that hESC are "high-grade ethics 'products'" as defined above, so that the handling and testing of these products have to be conducted only by teams who have received authorization for working with hESC.

The second bank vision is based on the model of Tissue Engineering activities, i.e. as a unified category of transformed biological *products*. It takes into account the idea of the variability of biological materials and the needs of benchmarks in order to deliver performing products to requesting teams. This model has the support of persons who believe that hESC products are detached from the growth and from the fate of the embryo. These products can be handled and processed outside the site of the requested team, and it should be possible for the bank to give an objective measure of the delivered products' efficacy. This model assumes a close link between practitioners and policymakers as well as industry regarding the setting up of protocols and guidelines.

Thus, France currently does not go further than an ongoing reflection between researchers and agency members regarding the setting-up of a national stem cells bank (Gottweis, 2008; Gottweis et al, 2009). No concrete actions have been made. But whatever would be the decision if one is adopted, it would have to be managed according to the set of fundamental rights protecting the human body and its elements, especially the principle of "non-patrimonialité", and according to the specific regime enforceable for hESC.

3. Conclusion

The semantic assimilation or connection between cells on the one hand, whether embryonic or somatic, and the integrity of the human body on the other, remains at the heart of discussions about the morality of how societies' regulate human materials for research or therapeutic development. We have shown how the current organisation of regulatory regimes in France and the UK currently diverge widely, and that there are a variety of pressures shaping the regulatory environment, including both scientific standard-setting with inter-national implications, and legislation emanating from national and EU bodies.

The EU has developed over-arching regulation which, as we have seen, may undermine the French principle of 'non –patrimonialité'. In France, part of the discussion about a stem cell bank revolves around the fram-

ISSN: 1989-7022 DILEMATA, año 3 (2011), nº 7, 17-37

ing of the technical issue of 'differentiation' of stem cells. Each line is grown according to the protocols acknowledge by the French Biomedicine agency. The difficulty for providing a stable legal definition of derived products obtained from line cultures significantly decreases the likelihood of a consensual and shared model of stem cell bank in France. Therefore, this kind of organization does not have a key role in the regulation of cellular research in France because this case-by-case authorisation does not lead to the production of shared standards of practice generalizable to all cell-therapy practices. This impedes the development of multilateral cooperation, such as is the case in the UK

The UK's National Stem Cell Bank has developed standards of good laboratory practice and has become highly regarded in Europe and worldwide. This central form of organization may not be one that other countries will adopt. The UK model enshrines a basic principle of informed consent that applies equally to development of cell therapy medicinal products. As a non-legislating regulator, the UKSCB takes notice of the legality of the operations of donor institutions in terms of host country laws, thus implementing EU law. It may be that the high public visibility of the UKSCB, from a sociological perspective, gives this institution an international status near the top of a hierarchy of regulatory credibility, which will have a spillover or 'trickle down' effect on the regulation of cellular research and product development more broadly. We have shown the dual position adopted by the EU: on the one hand encouraging the circulation of cell products which could benefit the European population, on the other hand a principle of prudence regarding the national positions on embryonic stem cells positions. With respect to the various domestic laws in Europe regarding the possibility of performing research on hESC, the various European legal instruments have said more on the "products" than on agreed fundamental principles to be respected to manufacture them. Nevertheless, in 2008, the Biobanking and Biomolecular Resources Research Infrastructure (BBMRI) project started. It was the first European Research infrastructure project funded by the European Commission, and one of its missions was "to have sustainable legal and financial conceptual framework for a pan-European Biobank infrastructure". BBMRI will be implemented under the legal entity of the European Research Infrastructure Consortium (ERIC). The expected start date is the end of 2011. While such infrastructure is not specific to stem cells, it shows a clear will of the EU to be involved in such activity beyond national stem cell banks. Moreover, the existence of a European registry for human embryonic stem cells[35] should be underlined as it shows a clear will of the EU to promote hESC research through the collection, organisation and sharing of information on hESC (Elstner and al, 2009).

DILEMATA, año 3 (2011), nº 7, 17-37 ISSN: 1989-7022

In the European Union, concrete actions have been undertaken which show a supra-national interest to develop biobanking infrastructure. The effect of this would probably be to spur Member States towards the setting-up of national biobanks.

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Notes

1. In this article, we use the term « stem cell » to refer to human cells acknowledged as such by stakeholders included in social controversies related to these biological products. This term should not be taken in a biological sense because the "stem" labeling is controversial among experts (Coulombel, 2009).

ISSN: 1989-7022 DILEMATA, año 3 (2011), nº 7, 17-37

DILEMATA, año 3 (2011), nº 7, 17-37 ISSN: 1989-7022

2. Discussion with Professor Anna Veiga during the Regenerative Medicine in Europe (REMEDiE) Closing Conference, "Bringing Regenerative Medicine to the Clinic: Trials and Tribulations in Europe and Beyond", April 18-19 2011, University of the Basque Country, Bilbao, Spain.

3. Since 1992, the EU developed a strategy for public health. (MICHEL, 2003-2004)

4. Law n°2011-814 of 7 July 2011 on Bioethics, French OJ n°157, 08.07.2011, p. 11826, text n°1.

5. Distinction is made in the French law between « therapeutic progresses » and « medical progresses », see below.

6. See notably Regulation (EC) N°1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) N°726/2004, OJ L324, 10.12.2007, pp.121- 137 and "A call to make valuable innovative medicines accessible in the European Union", Recommendations for a coordinated action to stimulate, measure and valorise pharmaceutical innovation, Background report for the ministerial conference, 23-24 September 2010.

7. Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells, OJ L 102 , 07/04/2004, p. 48- 58.

8. Commission Directive 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC as regards certain technical requirements for the donation, procurement and testing of human tissues and cells, OJ L 38, 09/02/2006, p. 40-52 and Commission Directive 2006/86/EC of 24 October 2006 implementing Directive 2004/23/EC as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells, OJ L294, 25.10.2006, p. 32- 50.

9. Article 168 of the Treaty on the functioning of the European Union, OJ C83, 30. 03. 2010, pp. 47-199.

10. Whereas (7) of the directive on tissues and cells. However, tissues and cells used as an autologous graft within the same surgical procedure, blood and blood components and organs or parts of organs if it is their function to be used for the same purpose as the entire organ in the human body are out of the scope of the directive according to its article 2.2.

11. Whereas (12) and article 4.3 of the directive on tissues and cells.

12. Article 12§1 of the directive on tissues and cells.

13. Article 13§1 of the directive on tissues and cells.

14. Article 12§2 alinea 2 of the directive on tissues and cells.

15. Article 14§3 of the directive on tissues and cells.

16. Law n°94-654 of 29 July 1994 « relative au don et à l'utilisation des éléments et produits du corps humain, à l'assistance médicale à la procréation et au diagnostic prénatal », French OJ n°175 of 30 July 1994, p. 11059; and Law n°94- 653 of 29 July 1994 « relative au respect du corps humain », French OJ n°175 of 30 July 1994, p. 11056.

17. Article 16-3 of the French civil code.

18. Article 16-5 of the French civil code.

19. See below point 2.

20. In practice it is only allowed to perform hESC research on supernumerary embryos and under the following conditions (Public Health Code Art. L. 2151-5): The relevance of the scientific project has to be demonstrated; Research should allow major medical progress; It is established that

ISSN: 1989-7022 DILEMATA, año 3 (2011), nº 7, 17-37

it is impossible to reach the expected result not using human embryos, human embryonic stem cells or stem cells lines; The research project and the conditions of its implementation are following ethical principles relating to embryonic and hESC research.

21. This Act only regulated removal of organs from cadavers and the requirements for informed consent by relatives were considered inappropriate.

22. It shall be noted that health products based on human cells and associated to a medical device can also regulated by EU law as combined advanced therapy medicinal products: an ATMP which "incorporates, as an integral part of the product, one or more medical devices […], and its cellular or tissue part must contain viable cells or tissues, or its cellular or tissue part containing non-viable cells or tissues must be liable to act upon the human body with action that can be considered as primary to that of the devices referred to". Article 2.1 (d) of Regulation (EC) N°1394/2007.

23. Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use, OJ L159, 27.06.2003, p. 46- 94.

24. Regulation (EC) N°1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) N°726/2004, OJ L324, 10.12.2007, pp.121- 137.

25. Annex, Part IV, 2.2 of Commission Directive 2009/120/EC of 14 September 2009 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use as regards advanced therapy medicinal products, OJ L 242 of 15. 09. 2009, pp. 3 - 12.

26. Article 2 para. 1 of Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use, OJ L311, 28.11.2001, pp. 67- 128 as amended by Article 1, 2) of Directive 2004/27/EC, OJ L136, 30.04.2004, pp.34- 57; see also whereas (6) of Regulation (CE) N°1394/2007.

27. Whereas (6) and Article 28, 2) of Regulation (CE) N°1394/2007.

28. Article L. 5121-1- 12° of the French Public Health Code.

29. Article L. 1243-1 alinea 1 of the French Public Health Code.

30. Article 2 (a) of the regulation (EC) n° 1394/2007 on ATMP.

31. http://www.ukstemcellbank.org.uk/

32. Neil Stephens et al. , the UK stem cell bank : an institutional ecology, Cesagen project: http://www.genomicsnetwork.ac.uk/cesagen/research/therapiesandenhancements/projecttitle-,24751,en.html

33. Law n°2011-814 of 7 July 2011 on Bioethics, French OJ n°157, 08.07.2011, p. 11826, text n°1.

34. Following the proposal from the Biomedicine Agency, this term replaced "therapeutic progresses" in the new French Bioethics Law issued in 2011. The argument for changing the wording was to move to a broader concept (medical) which could allow the realisation of more fundamental projects on hESC.

35. http://www.hescreg.eu/