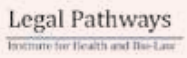
Governing Stem cells
Regenerative medicine in Europe

The vision and recommendations from the EUcelLEX project




Cell sources of advanced-therapy medicinal products (ATMPs)

Report and Recommendations

Judit Sandor
Jasper Bovenberg

1

In Work Package 2, our aim was to answer to the following questions: what are the interactions between EU and national legislation and the procurement of human (embryonic, foetal, and adult) stem cells for research, innovation and therapy and what are the effects of the application and implementation of that legislation on human stem cell procurement. Our main research methods included legal and comparative legal analysis which were applied in an empirical setting reflecting on the scientific and technological state of play in the domain. Our work was carried out with the specific end in mind of informing the Commission of the legal evidence basis that will enable the improviement and the optimisation of the innovative potential, the efficacy and efficiency, and the ethical soundness of future legislation in this area of bimedical research and innovation.

In order to ensure that our work remains evidence-based, we first generated data by collecting the main facts and figures relating to the state of play in stem ell research, regarding stem cell research, innovation activities in the domain, and relating to the specific stem cell therapies which were relevant to our work package. This also entailed reviewing both the current state of the medical art and of future needs for stem cells in biomedicine. The empirical review thus carried out defined the scope of our legal and comparative legal analysis by providing answers to the following questions: what type of stem cell are currently used, how and using what sources are they procured, what are the purposes of their use, what are the future applications planned (e.g.,

research, products, or therapies), what future needs for stem cells lie at the horizon, and what will serve as sources of stem cells in the future. The review exercise also enabled us to confirm or reject our preliminary classification of stem cells – human embryonic stem cells, foetal stem cells, and adult stem cells – which we planned to use in our legal analysis.

Stakes and stakeholder analysis

An integral part of assessing the interactions between legal regulation and the procurement of human stem cells was the determining of whether the available instruments properly address all stakes and all stakeholders concerned. The empirical review mentioned earlier was carried out, in part, to inform this stakeholder analysis. In addition to the obvious stakeholders at the receiving end of stem cell technologies (i.e., researchers, patients, and industry), we focused specifically on stakes and stakeholders at the sourcing end of stem cells – women, parents, newborns, and society at large. We made this decision with the assumption in mind that the specific setting in which a specific type of stem cells may become available – for example, foetal tissue after abortion – may pose not one but multiple and perhaps conflicting ethical, legal, biomedical, and social issues and dilemmas (e.g., the decision to terminate pregnancy must not be influenced by demands for donated fetal tissue, let alone by the prospect of financial gain). Overall, the stakeholder analysis produced a comprehensive overview, which relied on the different available cell types as the basis of its categorisations, of the stakes and the actors involved in the procurement of stem cells for research, innovation and therapy.

Mapping European legislation

Another focal area of our work was to identify and map EU and national legislation governing the sourcing and the procurement of human embryonic, foetal and adult stem cells. In this part of our research, we investigated not only legislation that deal with the procurement of stem cells directly, but also legislation the application of which influences the domain indirectly, for instance by influencing the availability of certain types of stem cells or of the intensity of stem cell-related innovative activity. This meant, for example, the inclusion of the provisions and the interpretation of Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions[1] in our mapping exercise, which by promising economic rewards through patenting, or by refusing access to those rewards, can influence procurement activities relating to certain types of stem cells. The EU regulation on advanced therapy medicinal products (Regulation 1394/2007/EC[2], hereinafter ATMP Regulation) was also included, even though prima facie it only deals with the

1 [1998] OJ L213/13.

2 [2007] OJ L324/121.

marketing authorization of industrially manufactured biomedical technology products.

Linking European legislation to stem cell procurement

Assessing the interactions between the relevant EU and national legislation and the procurement of human (embryonic, foetal, and adult) stem cells was a core objective of our research. The legal and contextual analysis carried out in this domain aimed to provide a detailed analytical overview of the relevant legal frameworks in place at the European and the national level, paying special attention to the implementation of the various pieces of EU legislation affecting the field indirectly. Our research extended beyond the narrower domain of legal regulation and included the relevant ethical guidelines, such as those produced in the opinions of the European Group on Ethics in Science and New Technologies and in the relevant decisions of different national ethics committees. We also looked at the relevant jurisprudence produced by different national and supranational courts. The geographical scope of our work was determined by the countries represented in EUCellLEX, which meant that we covered the laws in Belgium, Canada, France, Germany, Hungary, the Netherlands, and the UK. The legal framework of further countries was included when that was deemed necessary for the purposes of the comparative legal analytical work.

Main findings

Our work in the earlier introduced research areas within our work package produced the following main findings.

The EU ATMP framework

The ATMP Regulation was adopted to create an integrated European market for advanced therapies medicinal products by establishing for developers a distinct centralised development and marketing authorisation pathway within the European Medicines Agency (hereinafter, EMA) framework. Its efforts to satisfy stakeholder expectation and to vitalise the ATMP sector have, however, been hindered by

the challenges of regulating a market characterised by stakeholder vulnerability, uncertainty, rapid evolution, and ethical diversity. While at the level of regulatory paradigms and techniques the ATMP Regulation is a acceptably solid, there remain considerable doubts concerning whether it has managed to address the problems and the needs of the ATMP sector appropriately. It seems that for developing an integrated market for ATMPs the EU must first reassess the impediments to the successful commercialisation and translation of such products and address the issues of fragmentation and uncertainty in the ATMP field.

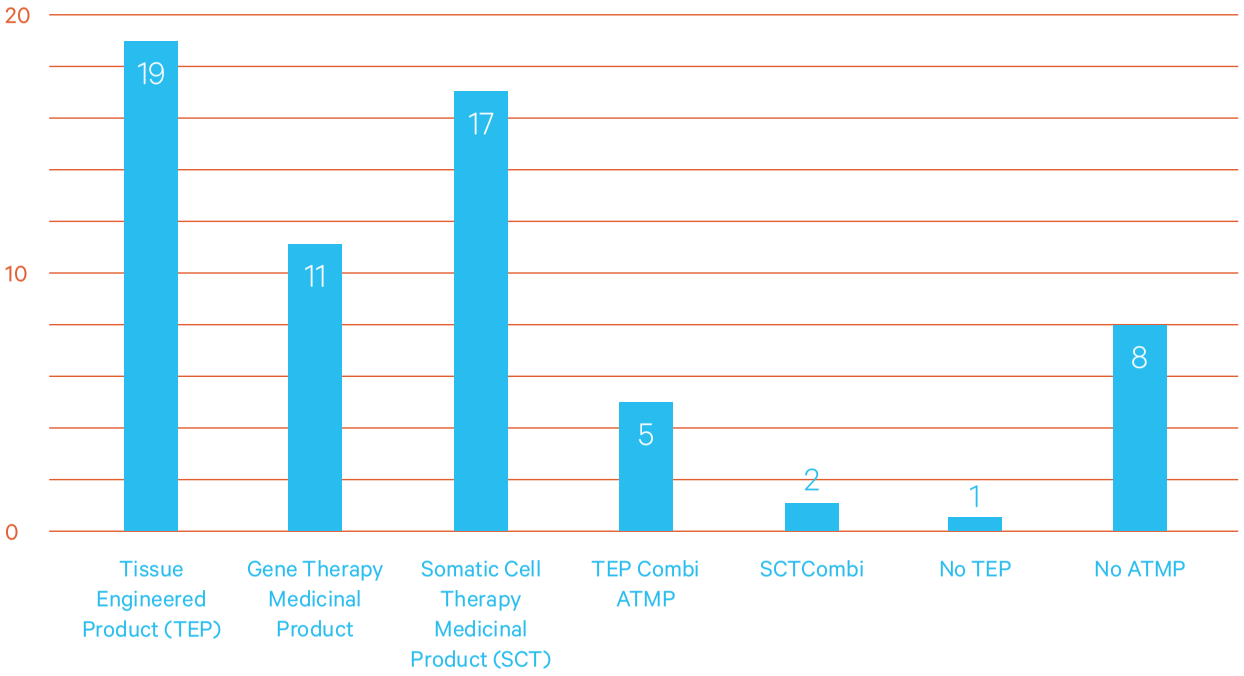
According to the evaluation of the ATMP Regulation, *prior* to its entry into force, the EU Member States had reported 31 ATMPs as being legally available in the EU market. *After* the entry into force of the Regulation, so far only 4 ATMPs have been granted a marketing authorisation, out of 10 applications. Meanwhile, a significant number of existing ATMPs continued to be used *without* a marketing authorisation under the derogations granted for the Member States (the hospital exemption or other). The marketing authorisation of one autologous product was suspended recently. Confronted with these figures, the European Commission is now considering, among other measures, the possibility of revising the requirements of the Regulation, especally those relating to autologous ATMPs which, as a result of their characteristics, may be subjected to a more relaxed regulatory treatment.

The majority of ATMPs with a marketing authorisation, with a classification obtained from the Committe on Advanced Therapies (hereinfafter, CAT) established within EMA, or in a clinical trial phase in the EU are autologous rather than allogeneic products. This is in line with figures for cell therapies in clinical trials worldwide.

The differentiated regulatory treatment of autologous ATMPs had already been discussed when the ATMP Regulation was prepared. At that time, a regulatory distinction between autologous and allogeneic products was dismissed as being artificial and unnecessary. Consideration was given neither to the characteristics of autologous therapies, nor to any fundamental distinctions between autologous and allogeneic products. The Commission adopted the position that the issue of reducing administrative burdens for small developers in the ATMP market, which tend to produce autologous products, was best addressed by the hospital exemption allowing small-scale product development. In

the ATMP Regulation, which treats autologous and allogeneic products the same, the cell source of an ATMPs (autologous, allogeneic, or xenogeneic) is only taken into account as one of multiple factors in the risk assessment of ATM products.

The main characteristics of autologous products include that the cell is the active therapeutic agent, short shelf-lives, complex supply logostics due to clinically limited time for testing, persistent issues related to variability of the donor-derived starting material (both intra- and inter-individual), and constant changes of the product in response to its environment. One of the regulatory implications of these characteristics is that the requirement to demonstrate comparability in the product authorisation process is an nearly unsurmountable barrier.



Classifications by EMA-CAT of ATM products submitted for classification in the pediod betweeen 01/07/2011 and 29/10/2014.

In the EU ATMP framework, regulatory flexibility and adaptability, which is a central demand towards technology regulation alongside the conflicting demand of providing clarity and predictability, were

sought to be ensured by placing at the centre of the marketing authorisation process the assessment of products by the CAT. The participation of the CAT should, in principle, ensure that cutting-edge scientific and technological knowledge are integrated into pre- and post-marketing assessments and controls. The CAT was designated a number of tasks in order to fulfil this role. Firstly, it is available for consultations on "any scientific assessment" of ATMPs regarding their quality, safety and efficacy. It may also give advice to developers to determine whether their product qualifies as an ATMP. The CAT may be required to assist in the production of any further policy documents necessary for the effective application of the legal framework. Finally, it may be requested to provide general advice to the EMA or to the Commission on ATMPs [3].

[3] The full list of tasks is regulated in Art.23.

This choice of ensuring regulatory flexibility and adaptability through the involvement of an expert committee raises a number of controversies from a legal and regulatory perspective. The CAT is endowed with considerable discretion in matters requiring scientific and technological assessment the boundaries of which are affected by the uncertainties of the applicable science and also by inevitable progress in science and technology. Arbitrariness in CAT assessments – both in a substantive and in a procedural sense – is, therefore, very difficult to control in law, and there are not many guarantees available which ensure under the current regulatory framework that marketing authorisations are issued without undue delay following an adequate assessment of the product concerned. From the perspective of the CAT as an institutional actor at the centre of the marketing authorisation process, the risk of failing to meet unmet medical needs may be smaller than that of allowing an unsafe, ineffective or low quality ATMP to enter the market. Thus, it may have a vested interest in slowing down the commercialisation of scientific advances and in erecting entry barriers to the market based on science. It may also be of relevance that the earlier mentioned different roles of the CAT serve as a constant source of conflict of interest situations affecting its operation.

Decision-making by the CAT is affected in particular by the following of interest scenario. On the one hand, it is required to incentivise and support developers so as to ensure their effective compliance with the applicable rules, for instance by giving them guidance before they apply for a marketing authorisation. On the other, when examining applications for a marketing authorisation, it proceeds in an essentially administrative process as the assessor of the safety, quality and efficacy of the products prepared by the

same developers. The dilemma here is that while the effective operation of the regulatory framework may demand a cooperative relationship between the EMA and developers, the significant legal and financial consequences for developers of the CAT's intervention in its different roles may require regulating a more formal and legally more accurately defined relationship between them. In the current framework, it falls ultimately on the legal remedies against the decisions taken [4] to ensure that the participation of the CAT was appropriate. The pressure on the legal remedies made available is considerable as they provide the only form of control over the balance established between regulatory flexibility and adaptability, on the one hand, and regulatory clarity and predictability, on the other.

The ATMP Regulation, so that a legislative text can be prepared and the measure can be adopted in the EU political process, relied heavily on the techniques of legislative cross-references and legislative deference. The integration of ATMPs into existing frameworks of EU medicinal products regulation was ensured by cross-references to the relevant pieces of EU legislation and the ethical issues of ATMPs were addressed by means of legislative deference to the relevant national rules. These gave a framework character to the ATMP Regulation which suggests that the EU legislator was unable – perhaps unwilling – to provide a comprehensive regulation of some of the substantive issues of the domain at the EU level.

While the cross-references to other sources of European medicinal products law enabled the necessary combination of the centralised and decentralised structures of market regulation in the EU, they also brought with themselves uncertainty and complications in the application of the law. The cross-references themselves are unable to ensure that the decentralised regulatory frameworks for medical devices, clinical trials and tissue and cell procurement operating at the national level will be successfully integrated into the centralised ATMP framework. These linkages with decentralised regulatory frameworks, which are subject to EU harmonisation [5], could jeopardise the centralised marketing authorisation framework for ATMPs by posing a threat to the integration of the new market and reinforcing or reintroducing diversity and fragmentation there.

The treatment of the ethics of the ATMP market by means of legislative deference to the relevant national legal instruments, while it is functional and simple as a regulatory technique, practically draws

4 Regulated in Arts 9 and 10 of Regulation 726/2004/EC Laying Down Community Procedures for the Authorisation and Supervision of Medicinal Products for Human and Veterinary Use and Establishing a European Medicines Agency, [2004] OJ L136/1.

5 See Directive 2004/23/EC on Setting the Standards of Quality and Safety for the Donation, Procurement, Testing, Processing, Preservation, Storage and Distribution of Human Tissues and Cells, [2004] OJ L102/48, Directive 93/42/EC Concerning Medical Devices, [1993] OJ L169/1, Directive 2001/20/EC on the Approximation of Laws, Regulations and Administrative Provisions of the Member States Relating to the Implementation of Good Clinical Practice in the Conduct of Clinical Trials on Medicinal Products for Human Use, [2001] OJ L121/34.

a veil over fundamental conflicts capable of destabilising the ATMP sector, such as that between the market paradigm pursued by EU legislation and the applicable bioethical standards which prohibit the objectification, instrumentalisation and commodification of human biological material. This is further exacerbated by the fact that despite the availability of overarching legal instruments, such as the Oviedo Convention on Human Rights and Biomedicine [6], the ethical standards of human medical biotechnology and its commercialisation are regulated in the different European countries in a different manner and in a diverse cohort of national regulatory instruments [7].

The choice of legislative deference, which provides for a decentralised treatment of the relevant ethical issues, is, thus, in conflict with its centralising intentions followed in order to establish an integrated ATMP market. Expecting developers to comply with both sets of rules and making them to deal with the diversity of ethics-based regulation at the national level seem to contradict the message of the EU policy that market participants should look at Europe and the EMA when aiming to enter the European ATMP market. Developers can be disfavoured, on the one hand, by separating as a matter of compliance and its location the ethics-based rules from the applicable technological rules. Also, developers involved in cross-border activities in a declaredly integrated market must comply simultaneously with multiple ethics-based regulatory regimes in the states affected. It, thus, seems that the ATMP Regulation not only has legitimation problems because it leaves the relevant ethical issues unaddressed, but, as a result of national ethical diversity capable of impeding innovation and development, it may also fail to deliver the promised public benefits (i.e., the availability of therapies) which are expected to provide an alternative legitimacy-basis for EU regulatory intervention.

National regulatory frameworks

The procurement of stem cells for research, innovation, or for therapeutic purposes is subject to fairly extensive regulation in Europe. In majority, the relevant measures deal with issues which relate to stem cell procurement only indirectly. These are issues which usually appear in the regulation of emerging biomedical technologies, such as risk, quality and safety, the ethics of biomedicine and biomedical research, or the achievement of public health objectives. Stem cell technology- or stem cell procurement-specific measures are rare, and they address matters which have direct connection with

6 CETS 164.

7 The legal deadlocks which may follow from ethical and legal diversity at the national level concerning the use and the commercialisation of (products containing) human biological material can entail that the same product in the different phases of its development and of its translation into therapies receives contradictory assessments at the European level and in the different Member States. This in turn erodes the central promise of the ATMP Regulation of regulatory predictability and consistency and undermines the core objective of integrating national markets and establishing, thereby, a level playing field for stakeholders.

the procurement and the use of stem cells in biomedicine, the most frequently regulated of which is the determining of the permitted sources of stem cells. In most countries, these and other relevant issues are regulated as an integral part of broader measures regulating generic domains, such as assisted reproduction, tissue and cell donation, or biomedical research. The few instruments dedicated to stem cell technologies and procurement address the issues prioritised in the local bio-legal discourse, such as the availability of supernumerary human embryos for stem cell procurement.

The national regulatory frameworks governing stem cell procurement are essentially mixed regimes combining, although in a variety of ways, generic and stem cell technology-specific provisions[8]. The national measures are predominantly generic in their content. The stem cell-specific norms, if available, were introduced in order to complement existing frameworks regulating general areas of biomedicine, such as assisted human reproduction. It is rare that stem cell procurement is regulated in self-standing rules in a separate instrument. The different national regimes, although they operate with comparable rules serving similar objectives[9], determine the focal points of regulation, develop their detailed rules, and choose between generic and technology-specific provisions differently. They differ in the regulatory strategy selected, the biological level regulated, and even in addressing the particular question whether stem cell technologies and technologies of stem cell procurement should be considered as areas requiring targeted regulatory intervention[10]. They use different bio-legal categorisations and concepts, and differentiate between the different stem cell technologies, regulate the different sources of stem cell procurement, and govern its broader biomedical context in distinct ways. Their mixity and diversity suggest that many of the issues of stem cell procurement, and of stem cell technologies themselves, are not specific to the technology which would then require targeted regulatory intervention. It is also clear that well-defined and well-operated generic measures governing the broader environment of stem cell procurement are just as important as adequately targeted technology-specific provisions.

8 Regulatory unevenness was clearly an issue in most of the national regimes. On the one hand, there were issues which received prioritised regulatory attention (for example, the donation of supernumerary embryos). On the other, some issues which have similar importance from the perspective of the general objectives of regulatory intervention continue to suffer from under-regulation (for example, the non-commercialisation principle). Some of this unevenness is, necessarily, the result of uncertainty as to the future application of rules in a new technological context which can justify caution when introducing detailed rules. For example, it is uncertain how in the context of the procurement of hES cell lines the restriction concerning the separation of the cells of the human embryo, introduced originally in a preimplantation genetic diagnosis context, will play out.

9 Partly as a result of EU harmonisation. The key measure is the Tissues and Cells Directive which regulates issues, such as risk, quality and safety, and the related institutional and procedural arrangements.

10 The legal measures adopted distinguish, either directly or indirectly, between the main types of cells and stem cells, such as adult cells, blood stem cells, totipotent and pluripotent stem cells, but they very rarely engage closer with stem cell technology, for instance by distinguishing between hES and iPS cells, and tend to keep their prohibitions and permissions at a more general regulatory level.

Austria	Act on medical assisted reproduction	ct on tissue quality and safety		
Belgium	Act on medically assisted reproduction and on the fate of supernumerary embryos and gametes	Act on the procurement and use of human bodily material for medical purposes and for purposes of scientific research	Act on research on in vitro human embryos	
France	Public Health Code			
Germany	Embryo protection act	Stem cell act	Transplantations act	Transfusions act
Hungary	Act on health care			
The Netherlands	Embryo act	Foetal tissue act	Act on the quality and safety of body material	Act on medical research on human subjects
The United Kingdom	Human tissue act	Human Fertilisation and Embryology Act 1990		

The national measures available to regulate stem cell procurement.

Only a few national regulatory systems intervene at the level of stem cells, and even fewer at the level of hESC or iPSC[11]. The majority of them focus on the protection of human embryonic life addressing that issue in the general context of biomedical research and/or human assisted reproduction[12]. Only some put particular emphasis on regulating in detail the corresponding institutional and procedural environment. Even though the foundations, such as the commitment to protect the value of human (embryonic) life and of human biological material and the dedication to safeguard human integrity and autonomy (and self-determination), are similar and shared, the different national instruments reveal considerable local differences[13]. The local context has had a considerable influence on the detailed regulation of generic regulatory issues, such as informed consent, the information rights provided to individuals, the prohibition of financial gain, the prohibition of commercially-oriented conduct, the

11 Germany: the Stem cell act (on pluripotent human stem cells) and the Transfusions act (on blood stem cells). See also the Dutch Embryo act's limited hESC-related provisions, and the provisions of the French Public Health Code and of the Belgian Act on the procurement and use of human bodily material on hESC.

12 Separate laws for the protection of human embryos were adopted in Belgium, Germany, and the Netherlands. This does not mean that human embryonic life would not be protected in more general legal measures in other countries. France represents a specific case as all relevant rules on medicine and biomedical research are regulated in the general Public Health Code, which has specific provisions on human embryos and human embryonic stem cells (hESC), on human assisted reproduction and supernumerary embryos, and on the procurement and the donation of human biological material. The Hungarian act on the protection of human embryonic life (Act 1992:LXXIX) focuses solely on in vivo embryos and foetuses, and regulates the termination of pregnancies.

13 This is most visible in the regulation of permitted sources of stem cells. There are restrictive regimes, such as Austria or Germany which strictly limit potential sources of stem cells, medium regimes, such as Hungary, the Netherlands, or France which exclude certain, ethically controversial sources of stem cells based on value-based considerations, or liberal regimes such as the UK or Belgium which recognise a broader spectrum of legitimate sources of stem cells.

requirement of purpose-bound and proportionate human intervention, and the requirement to adhere to scientific standards in biomedical research.

The introduction of stem cell-specific instruments, when that was considered as necessary, and the alternative of introducing stem cell-specific rules into generic measures seem to have followed different objectives in the different states. Protecting - mainly in vitro – human (embryonic) life serves as the main regulatory objective in most states, either explicitly (for example, Austria, Germany, Belgium and the Netherlands)[14], or implicitly (the UK and Hungary)[15]. Advancing healthcare and biomedical research are presented as parallel objectives in a number of countries[16]. Regulating stem cells and their application appeared as a specific objective in a few states (for example, Germany, Belgium and France)[17]. The regulation of stem cell technologies, stem cell procurement in particular, as part of comprehensive codes governing health care and biomedical research, as in the case of France, necessarily means that regulatory intervention is subject to multiple and overlapping objectives with specific objectives influencing the regulation of particular domains within the code, such as the protection of the persons involved in donation, the regulation of tissue and cell procurement, or the availability of human embryos for reproductive or for biomedical research purposes[18].

The incorporation of the relevant bioethical considerations – often rather explicitly and through restrictive or prohibitive rules – is a central component of biomedical technology regulation in Europe. These considerations determine the core distinctions introduced in regulation and the regulation of restrictions and prohibitions concerning the relevant human activities. The most relevant regulatory distinctions concern the use of human biological material, including human embryos[19], and involve distinctions between uses in a parental project (in an assisted reproduction process) and for other purposes, such as biomedical research or therapy, or education[20], between permitted (authorised/licensed) and prohibited (non-authorised/non-licensed) uses, or between primary and secondary uses of human biological material. A similarly crucial distinction is that made between in vitro and in vivo interventions and between in vitro and in vivo human biological material, especially between in vitro and in vivo human embryos. The distinctions between living and deceased persons in donation, and between adults, minors and persons under legal guardianship, representing different states of personhood, also have significant ethical relevance. Further relevant regulatory distinctions include

14 And the protection of the woman involved (Germany, the Embryo protection act). The Belgian rules have a strong focus on the regulation of the fate of supernumerary embryos created in a parental project. The Dutch Embryo act also contains extensive provisions on biomedical research using human embryos. The Netherlands has a separate act for the protection of human foetal life (the life of the human fruit) and for the procurement of human foetal tissue. The Austrian Act on medically assisted reproduction regulates this issue predominantly in the general technological context of human (assisted) reproduction.

15 The UK: Human Fertilisation and Embryology Act 1990. Hungary: Act on health care.

16 For example, Belgium, Germany and the Netherlands.

17 The Belgian Act on the procurement and use of human bodily material defines stem cells as cells of human origin capable of self-renewal and differentiation to one or multiple specialist human cells. The German regulatory framework relies on a distinction between totipotent and pluripotent (stem) cells when defining the human embryo and regulating stem cells. The Stem cell act defines pluripotent cells as all human cells which have the capacity for development through cell division and which can develop into different specialised cells, which, however, are unable to develop into a human being. hESC are defined as pluripotent cells harvested in vitro from a supernumerary human embryo. It also gives a definition to hES cell lines as hESC which are maintained in a cell culture or stored in a cryoconserved state. The Transfusions act defines blood stem cells.

18 Which may include other overarching objectives, such as the protection of the rights and the dignity of persons in health care (see Articles L1110-1 – L1110-3 of the French Public Health Code).

19 In Germany, also hESC (Stem cell act).

20 See the general distinction in Germany between the legitimate uses and misuses of biomedicine (Embryo protection act).

those between activities for the benefit of the individuals (donor) concerned and other activities, between necessary and unnecessary interventions, between scientifically and professionally sound and unsound interventions, and between research conducted following legitimate and illegitimate research aims. Hungary and the Netherlands regulate explicit distinctions between invasive and non-invasive interventions and between the intentional and non-intentional changing of the conditions of the research subject.

The national measures contain further, predominantly ethics-based [21] components relevant for stem cell procurement. The prohibition on financial gain is recognised in every national regime investigated. They are, however, far from uniform in regulating the costs available for reimbursement in the special context of cell and tissue donation and procurement [22]. Similarly, while the principle of informed consent is recognised in the different national laws, its details, for instance the actual scope of the consent given or the formalities of providing consent, are regulated differently [23]. A further shared requirement is that interventions, including the procurement of hESC, must be scientifically justifiable, conform with scientific standards, or be subject to scientific supervision [24]. Some states adopted a particularly detailed regulation of this requirement [25]. As a general benchmark, the regulatory systems investigated, although in different ways, require that human conduct in the biomedical research context must be proportionate and necessary [26]. The French regime provides an important locally specific example for the regulation of legally secured information rights of individuals and the parallel information obligations of the relevant institutional actors [27].

The national measures governing tissue and cell procurement, partly as a consequence of the implementation of the EU Tissues and Cells Directive, are characterised by a detailed framework for regulating risk, quality and safety. Generally, they focus on the conditions of tissue donation and procurement, on the rights of donors including informed consent, and on the obligations of institutional actors in the processing, storing, transportation and in the related administration of donated material. The risk, quality and safety rules in the different Member States are, however, by no means uniform. This is indicated foremost by the uneven practices of implementing the EU directive. There are national measures which achieved implementation without notable modifications (for example, Austria and the Netherlands) [28], there are others which implemented the directive with some structural adjustments so

21 The balancing of conflicting interests, the regulation of technological possibilities and scientific appropriateness are other factors addressed in these rules.

22 Austria: Article 16, Act on medically assisted reproduction; Belgium: Article 6, Act on the procurement and use of human bodily material and Article 48, Act on medically assisted reproduction; France: Articles L1211-4 and L1244-7, Public Health Code; Germany: Article 4, Stem cell act and Article 2, Transplantations act; Hungary: Article 170, Act on health care; the Netherlands: Article 3a, Act on the quality and safety of body material.

23 Austria: Article 8, Act on medically assisted reproduction; Belgium: Article 10, Act on the procurement and use of human bodily material, Article 8, Act on research on in vitro embryos and Articles 12 and 41, Act on medically assisted reproduction; France: Articles L1211-2, L1221-5 and L1231-1, Public Health Code; Germany: Article 4, Embryo protection act and Article 3, Transplantations act; Hungary: Articles 159 and 176, Act on health care; the Netherlands: Article 5, Embryo act and Article 6, Foetal tissue act; the UK: Schedule 3, Human Fertilisation and Embryology Act 1990.

24 Belgium: Article 3, Act on research on in vitro embryos; France: Article L2151-5, Public Health Code; Germany: Article 4, Embryo protection act; the Netherlands: Article 2, Embryo act.

25 Article 159, Act on health care.

26 Belgium: Articles 3 and 4, Act on research on in vitro embryos and Article 10, Act on the procurement and use of human bodily material; France: Article L-1211-6, Public Health Code; Germany: Article 4, Embryo protection act and Article 8, Transplantations act; Hungary: Article 164, Act on health care; the Netherlands: Article 3, Embryo act; the UK: Schedule 2, Human Fertilisation and Embryology Act 1990.

27 Articles L1211-2, L1244-7, L2141-4 and L2151-1, Public Health Code. See also in Germany Article 7, Transplantations act.

28 See Act on tissue and quality and safety in Austria and Act on the quality and safety of body materials in the Netherlands.

as to ensure that its requirements are duly integrated into existing national regulatory frameworks (for example, France and Germany) [29], and, finally, there are regimes which incorporated EU rules with both structural and substantive adjustments made to national law (for example, the UK and Belgium) [30].

The national regulatory systems all operate an institutional framework for the ethical and other expert (for example, biomedical or technological) supervision of stem cell-related activities, including stem cell procurement, and they provide for regulated procedures governing particular aspects of those activities, such as securing research authorisation or obtaining informed consent. Again, in part, this is the outcome of the implementation of the relevant EU obligations which, in regulating risk, and quality and safety, place considerable emphasis on putting in place effective institutions and procedures [31]. The national institutional and procedural settings, however, exhibit considerable variety as to the bodies established, the powers granted to those bodies, the allocation of responsibilities, the design of institutional rules, the regulation of the standards of conduct, the protection of the rights and interests of the individuals concerned, and in regards how institutional communication and information flow are organised [32]. Among the bodies established in the different regimes, we find national (and other) medicines agencies, ethical councils, biomedical research bodies, central registries, and other "responsible authorities". The national procedural rules, which aim to ensure that the powers available to the institutions, including enforcement and sanctioning powers, are exercised in an ordered fashion, subject to requirements of transparency and accessibility, and with due regard to the rights and interests of the parties, also reveal genuine differences as to the level of their detail and sophistication [33].

29 France: Book 2, Public Health Code. Germany: Transplantations act.

30 See Act on the procurement and use of human bodily material in Belgium and Human Tissue Act in the UK.

31 See Articles 16 to 28 of the EU Tissues and Cells Directive.

32 See, for example, the particular Dutch approach of framing the relevant prohibitions and permissions as institutional and procedural rules in the Embryo act. See also the particular national examples for regulating information rights and the corresponding institutional obligations, see note 65 above.

33 See the specific provisions in France on obtaining informed consent, the Dutch rules on obtaining an authorisation for the "research protocol", or the German approach of regulating the conditions of decision-making in the national institutional and procedural framework.

the powers granted to those bodies, the allocation of responsibilities, the design of institutional rules, the regulation of the standards of conduct, the protection of the rights and interests of the individuals concerned [...]

Recommendations for future regulation

Our recommendations for future regulation in the domain of stem cell procurement can be grouped into the following larger categories.

Regulation at EU level

- Having regard to the degree of differentiation in the stem cell domain, and in the ATMP market, in particular as a matter of the products regulated [34], the expectations of stakeholders, or the applicable ethical principles, the current choice between centralised and decentralised regulatory frameworks needs to be reconsidered [35].

- Whilst respecting the applicable constitutional principles, such as the principle of conferral, subsidiarity and proportionality, the areas EU intervention in substantive areas of regulation, where the Member States exhibit differences, such as non-commercialisation, or the information rights of inviduals, need to be reconsidered [36].

- Having regard to the particular characteristics and needs of stakeholders and of products and their use in the domain, the objectives pursued by EU level regulation, such as the creation of an integrated product market, need to be reconsidered [37].

- Having regard to the differences in regulating the details of otherwise common bioethical requirements, even in harmonised areas, further EU-driven sharing of best regulatory practices needs to be considered [38].

34 For example, the characteristics of autologous cell therapies trigger the question of whether they should be qualified and regulated as products subject to centralised marketing authorisation in the EU. The answer to this question may lead to the revising of the marketing authorisation requirements, or, seeking a more robust response, to the broadening of the so called hospital exemption under the ATMP Regulation so as to cover such preparations.

35 The current regulatory and governance arrangements in the EU are based on a combination of centralized and decentralized solutions which allocate powers and responsibilities on a territorial scale accordingly. Because of the risk of fragmentation and the possibility that the available centralized frameworks are undermined by their operation, in light of the practices followed in the different Member States, the existing decentralized arrangements need to be reviewed. This revision may provide the ground for a centralized and/or peer-to-peer coordination of national practices leading to the publication best practice documents and the formulation of benchmarks of conduct in non-binding recommendations. The review of centralized arrangements must also be undertaken. The practices of centralized European bodies must also be reviewed with special attention paid to their transparency and to the possibility of developing further stakeholder-friendly regulatory solutions.

36 Also, current EU regulatory frameworks, while they acknowledge the human rights implications of regulating stem cell technologies, they defer

Regulation at Member State level

- Having regard to the diversity of national regulatory practices in this regard, the introduction of further stem cell technology- and stem cell procurement-specific measures needs to be considered [39].

- Having regard to the state of the applicable permissions and prohibitions as laid down in legislation in the different states, the clarification of the applicable stem cell-specific boundaries needs to be considered.

- Having regard to the crucial role played by-non-stem cell specific regulation in the regulation of stem cell technologies and stem cell procurement in particular, the reassessment of such generic measures in light of the specificities of stem cell technologies needs to be considered [40].

- Having regard to the fact that some Member States have advanced regulatory solutions in place in different areas of regulation, cross-border regulatory learning and borrowing, in parallel with EU-driven best practice sharing, need to be considered.

the regulation of those issues to the national level. While this practice is justifiable on grounds of competence issues, questions of subsidiarity, and of safeguarding Member State diversity, the deference clauses in the relevant pieces of EU legislation assume perhaps too readily that individual Member States are able to regulate the relevant matters adequately. It may be preferable to provide deference to national law whilst maintaining some form controls over national legislation or a power of regular scrutiny over national practices stemming from those laws. The EU Charter of Fundamental Rights may provide, beyond general references in legislation to its existence, a basis for a Union-level regulation of some of the human rights issues arising.

37 If the free movement of the product to (cross-border) patients cannot be achieved, because (i) the cell therapy product is, in essence, a bed- or hospital-side, non scaleable and non-moveable product and/or (ii) the cell therapy product is such that it cannot meet marketing authorisation standards (comparability), then regulation should focus on the free (cross-border) movement of patients to the product (prepared at point of care, on hospital exemption quality and safety standards).

38 Having regard to the variety of national regulatory solutions, it would be difficult to identify a single best regulatory approach or regulatory solution. The national regimes all have stronger and weaker components both in generic biomedical and in stem cell-specific regulation. There is, thus, a broad scope for improving national regulatory mixes by way of borrowing from other regimes. This must, however, be carried out with care as regulatory intervention can increase as well as decrease the access of patients to therapies and can enhance as well as reduce justice and equity in the health care domain through regulating access to novel therapies. This responsibility, in our view, instead of diminishing, increases the need for learning from other regulatory regimes.

39 When regulating human conduct on the basis of stem cell technology-specific considerations, special care must be taken of the clarity of the language and of the use of appropriate

Regulatory challenges

- Having regard to stakeholder needs, the calibration and administration of regulatory flexibility and adaptability enabling stakeholders to introduce new scientific and technological developments under the exisiting regulatory framework, both in EU and national legislation and both in generic and stem cell-specific measures, need to be reconsidered [41].

- Having regard to the legal and economic impact of the applicable regulatory framework on stakeholders and to legal implications of the future use of products and therapies in human biomedicine, the balance between regulatory clarity and predictability and regulatory felxibility and adaptability need to be reconsidered [42].

- Having regard to the different objectives pursued and to stakeholder needs, the application of different regulatory modes, such as co-regulation, self-regulation, steering through soft-regulation, needs to be considered.

- Having regard to the legal and economic implication of CAT decisions and the prevalence of conflict of interest situations before the CAT, the protection provided by the current remedial framework needs to be reassessed and the introduction of further legal safeguards, whilst accepting the necessity of the CAT playing multiple roles, needs to be considered.

terminology which is informed of the technology as well as of its ethical implications. Otherwise, even issue-specific regulatory instruments (i.e., a stem cell act) may only increase legal uncertainty or lead to unintentionally restrictive rules or rules which are open to restrictive interpretation. It must be taken into account, however, that clear and technologically-informed legal terminology and regulation may prevent recognizing scientific and technological developments on the boundaries of science and technology. Alternatives to legal regulation, whereby more open, discursive forms of regulation may be given room, or where the emphasis is on helping stakeholders through the relevant (e.g., licensing) processes, may need to be considered even at the European Union level. Some of the implications of the applicable ethical principles (e.g., commercialization of research results) may require further regulatory efforts, potentially at the European-level so that at least minimum legal, or even non-legal, benchmarks are available for stakeholders.

40 There is a need to increase clarity and regulatory detail in the existing frameworks regulating the commercialization of the human body, consent, data protection, privacy, or the use of human embryos in stem cell technology, which are either generalist in terms of the rules they contain and lack a stem cell technology-specific angle, or are general principle-based lacking details as to their application in specific circumstances.

41 This must be carried out with a view to the uncertainties of translation into therapies, where there may be more unknown unknowns than known unknowns, which affects the speed of translation activities and damages collaborative research efforts covering multiple jurisdictions.

42 Regulating the human rights implications of stem cell technologies, in case it is necessary to complement technology regulation with this element, requires, on the other hand, a higher degree of regulatory stability, clarity and predictability, especially when the violation of the relevant rules attracts criminal or administrative penalties.

Stem cell use

Michael Morrison
Jessica Bell
Rosario Isasi
Jasjote Grewal
Koko Kwisda
Nils Hoppe
Jane Kaye

The overall aim of this work package was to understand how the current regulatory framework within the European Union affects how stem cells are being utilised by institutions based in EU member states. This work was organised into three components. Firstly, the landscape of stem cell use from basic research was surveyed from initiatives to bank, disseminate and characterise stem cells through to therapeutic innovations and regenerative medicine with the aim of assessing the scope of stem cell research and to identify relevant trends. The second step was to identify and analyse regulatory mechanisms (in a broad sense) that govern these uses of stem cells. The third component then brought these elements together, drawing on additional input from relevant stakeholders in stem cell science and regenerative medicine, to understand how the current regulatory landscape interacts with the application and translation of stem cell science. This identified emerging challenges and unmet governance needs which have informed our recommendations for policy and further research.

The most widespread use of human stem cells is still as research tools for biological and biomedical research. As with cultured human and animal cells before them, stem cells provide a means for scientists to investigate the basic properties of living biological systems including the role and function of genetic and epigenetic elements, organelles and other molecular components (Landecker 2007). In addition to exploratory research there are several major translational trajectories for stem cell research. One of the most longstanding potential applications of stem cells is in cell therapy. Stem cells' capacity to generate some or all of the cell types found in the human body means that stem cells could be used to repair damaged tissue in a wide range of diseases including major chronic conditions such as cardiovascular disease, diabetes and neurodegenerative disorders. At present, the only routine use of stem cells to treat disease is the use of bone marrow or cord blood stem cells to treat blood cancers. Many potential regenerative medicine applications currently under investigation incorporate stem cells with other technologies including bio-scaffolds that provide a three-dimensional surface to which the cells can adhere; 'bio-printing' technologies that are beginning to be able to generate more complex multi-layered arrangements of cells and tissues; and gene-editing to produce genetically modified cells for transplantation (Das 2016; Hochfield et al 2016). In recent years there has also been significant investment in pluripotent stem cells for in vitro disease modelling (sometimes described as 'disease in a dish' applications) and as tools for assessing the toxicology and biological activity of small molecule drug compounds (Heilker et al 2016; Inoue et al 2014; Suter-Dick et al 2015). There is a significant expectation in the latter case that stem cell-based toxicology technologies could lead to a reduction in the use of animal models in drug discovery and testing. These two applications are related, at least at the current stage of research, as they both require reliable techniques for differentiating pluripotent stem cells into a range of adult tissue types, for example cardiac cells, nerve cells or liver cells. The latter have an obvious relevance for examining the prospective toxicity of novel compounds in human tissues. In vitro cultures of these differentiated human cells also provide a means for scientists to examine the behaviour and characteristics cells from tissues that are hard to access in living human subjects such as the heart or brain (see for example Heilker et al 2014). Again there is potential for stem cells to be combined with other technologies in these applications. An example currently under

development is the incorporation of living cells in micro-engineered laboratory models of human organs – so-called 'organ-on-a-chip' systems, which have potential applications in toxicology and understanding human disease (Esch et al 2015).

Within the public sector research using stem cells occurs in academic institutions, public hospitals and clinics, and within government laboratories. This research tends to cover all of the above applications and other minor avenues of exploration. In the private sector most large pharmaceutical companies have some investment in stem cell technologies, although this is not necessarily an investment in cell therapies *per se*. Biotechnology companies and private medical and research institutions are also involved in stem cell research, with much of the commercial development of cell therapies located in Small and Medium sized enterprises (SMEs) in the biotech sector. Biobanks in both public and private sectors play an important role in the stem cell economy, but their role in research is often limited to studies designed to improve the storage, quality control and characterisation of cells. There are also a number of emerging public-private ventures in the stem cell field, with calls for more investment in cross-sectoral ventures to address major translational challenges in regenerative medicine (Rao 2013; Bubella, Mishra and Mathews 2014; French et al 2014).

Within the overall landscape of stem cell research the following developments are particularly worthy of further attention:

Induced pluripotent stem cells (iPSCs)

The capacity to 'reprogram' differentiated adult cells into an immature, highly plastic 'pluripotent' state was first reported by Japanese scientists using murine cells in 2006 (Takahashi and Yamanaka 2006) and was repeated with human cells in 2007 (Takahashi et al 2007; Yu et al 2007). The reception among stem cell scientists at the time was also one of optimism, albeit tinged with caution and acknowledgement of contingency surrounding the new technology (Hauskeller and Weber 2011). One the one hand, iPSCs appeared to share the same biological plasticity that underpins the therapeutic promise of human embryonic stem cells, but without the often fraught political and ethical concerns that accompany the use, and destruction, of human embryos in biomedical research. At the same time,

the status of these novel cells was uncertain. Human embryonic stem cells (hESCs) remained the 'gold standard' for assessing pluripotency. Questions were raised about whether iPSCs were 'really' pluripotent (in comparison to hESCs), and whether they would prove sufficiently safe, efficient and governable to form the basis for human cell therapies (Belmonte et al 2009; Hu et al 2010). At the same time, governance frameworks such as the one in Germany pushed a significant proportion of hESC researchers into the iPSC field (or abroad) by way of restricting the creation and import of hESC cells (Wiedemann et al 2004).

Now, as the end of the first decade of research on human iPSC approaches there have been a number of significant developments in the field. Although most cellular reprogramming still requires a considerable amount of manual work at the laboratory bench, automated methods for producing iPSCs are beginning to emerge (Paull et al 2015). Scale-up and automation remain major bottlenecks in developing regenerative medicine as a viable commercial proposition (Gardner et al 2015), but a number of technologies are now available to routinize key tasks relating to iPSC quality and characterisation, including transcriptomic assays to assess pluripotency in human cells and SNP microarrays to compare the genetic identity of reprogrammed cells to the adult cells from which they were derived (Muller et al 2011). While the pluripotency of any particular attempt at reprogramming requires verification by assay, the capacity of reprogramming to generate pluripotent cells *per se* is no longer in question. In this regard iPSCs have benefited from the considerable work that went into defining and establishing international scientific standards for pluripotency and cell quality in hESCs (Webster and Eriksson 2008). Indeed a number of scientific articles have not started using the term 'pluripotent stem cell' (PSC) research to include hESCs, iPSCs and any future methods of producing pluripotent cells that might arise as a single research topic.

Having instigated the discovery of iPSCs, Japan remains at the forefront of developments in this field (Ilic 2016). The regulatory landscape in Japan has been significantly adapted to promote the adoption of iPSCs as the most suitable cell type for future regenerative medicine applications (Mikami 2014). In addition, the specially-established Centre for iPS Research and Application (CIRA) in Kyoto, Japan currently has some 75 clinical grade human iPS in its biobank. These are envisaged to form the basis for future human cell therapies. The first experimental applications of iPSC-derived cell therapies in

human patients are currently making tentative progress in Japan, although the first-in-human trial has not been without safety concerns (Kimbrel and Lanza 2015). The target diseases for these early iPSC applications are primarily degenerative diseases of the eye. The eye has a number of advantages in that it is a relatively small tissue and enjoys some separation from the main human immune system which can otherwise pose a risk of an immune rejection of transplanted tissues and cells (Kimbrel and Lanza 2016). These eye conditions have also shown considerable promise for hESC-derived cell therapies and may provide a future site where European, US and Japanese regulatory authorities will have to adopt practical requirements for safety and quality control of pluripotent cell therapies for human use.

Large-scale iPSC biobanks

Outside of Japan investment in iPSCs has also been significant. However, the interest of public and pharmaceutical industry bodies has arguably been more directed towards the development of iPSCs as tools for drug discovery and toxicology. This is reflected in a number of large-scale initiatives to produce, bank and disseminate human iPSCs (McKernan and Watt 2013). These include the New York Stem Cell Foundation Research Institute repository (reported to be aiming to bank 2,500 human iPSC lines), the Human induced pluripotent Stem cell initiative (HipSci) funded by the Wellcome Trust and the Medical Research Council in the UK (producing 700 iPSC lines from healthy volunteers and 100 disease-specific lines in its first phase), and two European consortia created through the EU Innovative Medicines Initiative are also focusing on human iPSC. The Stem cells for Biological Assays of Novel drugs and prediCtive toxiCology (StemBANCC) consortium aims to produce iPSC lines from skin, hair and blood samples provided by 500 chronic disease patients and healthy volunteers, while the European Bank for induced pluripotent Stem Cells (EBiSC) is collecting iPSCs produced through a range of existing projects to create a hub for quality assessment and dissemination of these cell lines. It is significant that the cell lines produced and banked by these projects are in large part not clinical grade lines. They are not intended to be used in future cell therapies but in developing stem cell-based platform technologies for disease modelling and evaluating the pharmacological and toxicological properties of novel compounds.

Having instigated the discovery of iPSCs, Japan remains at the forefront of developments in this field (Ilic 2016). The regulatory landscape in Japan has been significantly adapted to promote the adoption of iPSCs as the most suitable cell type for future regenerative medicine applications (Mikami 2014). In addition, the specially-established Centre for iPS Research and Application (CIRA) in Kyoto, Japan currently has some 75 clinical grade human iPS in its biobank. These are envisaged to form the basis for future human cell therapies. The first experimental applications of iPSC-derived cell therapies in human patients are currently making tentative progress in Japan, although the first-in-human trial has not been without safety concerns (Kimbrel and Lanza 2015). The target diseases for these early iPSC applications are primarily degenerative diseases of the eye. The eye has a number of advantages in that it is a relatively small tissue and enjoys some separation from the main human immune system which can otherwise pose a risk of an immune rejection of transplanted tissues and cells (Kimbrel and Lanza 2016). These eye conditions have also shown considerable promise for hESC-derived cell therapies and may provide a future site where European, US and Japanese regulatory authorities will have to adopt practical requirements for safety and quality control of pluripotent cell therapies for human use.

Developing new regulatory standards as evidence from stem cell based drug discovery platforms begins to complement, and potentially replace, evidence from preclinical animal testing is therefore another governance priority to consider. Of equal, but likely more immediate significance is that the large number of cell lines being made available by these banking projects has the capacity to dramatically increase the movement of human stem cell lines across national boundaries. This has implications for traceability and for the need to address issues of harmonisation across different regulatory regimes. Moreover, the value of human-derived iPSCs derives in part from the capacity to generate pluripotent cells that carry the genetic make-up of individual patients with conditions that scientists want to study. The utility of iPSC as tools for disease modelling increases with the amount of medical and genetic data about the original cell donor that accompanies the cell line itself. The rise of international iPSC traffic is therefore also likely to involve a rise in the sharing of sensitive personal data (as defined under the EU General Data Protection Regulation).

Public-private partnerships

Public-private consortia are emerging as a novel organisational strategy to address the challenges of translational research in many areas of the life sciences (Altshuler et al 2010; Lim 2014). This approach is seen as especially relevant in the fields of stem cell science and regenerative medicine (Rao 2013; Bubella et al 2014; French et al 2014). Prominent initiatives to promote the creation of such consortia include the Food and Drug Administration's Critical Path Initiative (CPI) in the US and the Innovative Medicines Initiative (IMI) in Europe (Vaudano 2013; Woodcock & Woosley 2008). Both the IMI StemBANCC and EBiSC consortia are public-private partnerships. These consortia involve academic scientists working in partnership with those employed by pharmaceutical and biotechnology companies and in some cases also with patient groups, regulators and other groups. Although there is variation across initiatives (and consortia) one of the major aims of these programmes specifically intended was to yield new tools, or platform technologies, that will be able to 'address specific challenges related to discovery, preclinical modelling, clinical validation, or risk-benefit assessment of new treatments' (Goldman 2013). To achieve these goals, large research collaborations depend on enhanced sharing of scientific data and knowledge but they can also present particular challenges to the very processes through which this occurs (Morrison et al 2015; Budin-Ljøsne et al 2014; Muddyman et al 2013). In addition, public-private collaborations work by operating in a pre-competitive space to produce resources that are communally available to public and private organisations. This has many benefits but it also potentially comes into conflict with traditional licensing arrangements for academic discoveries which have different licensing costs and terms depending on whether users are based in academic or commercial domains. Public-private partnerships can overcome this by paying the commercial licensing fees, but the greater challenge is likely to arise if such differentially licensed-technologies are themselves incorporated into communal resources produced by public-private consortia. An example is the use of CRISPR-Cas 9 gene editing technology which has different licensing arrangements for public and private end users. A resource of, for example, gene-edited stem cell lines produced by a public-private consortia could potentially have difficulty securing legal permission to make the lines available to all users on an equal basis, something that currently underpins arrangements like the European Union Innovative Medicine Initiative's funding.

Gene editing

The advent of CRISPR-Cas9 systems and related gene editing tools provide accessible and cost-effective means to permanently modify a genome, such that gene modification looks likely to become a standard method for addressing basic research questions. The Nuffield Council (2016) have deemed such techniques to have the potential to revolutionise the biological approaches to genetic diseases, suggesting that they represent a potential "tipping point" in genetic modification whereby the technology has developed to a point where it can precipitate significant change. A range of gene editing applications have been afforded particular public and media attention, including human germ line modification, directed evolution, the production of transgenic animals and the creation of genetically modified crops. In the rapidly growing number of publications that report use of CRISPR-Cas9 techniques, examples of its application to each of these purposes can already be found (Feng et al 2015; Liang et al 2015; Zou et al 2015; Miao 2013).

Gene editing of human cells, including stem cells also has considerable potential both as a research tool and with therapeutic applications. Combined 'gene and cell therapies' are likely to be closest to translation in the area of blood diseases, where the patient's blood cells can be extracted, modified using CRISPR technology, expended, checked for safety and quality and then re-implanted (Reardon 2014; Cyranoski 2016). Application of gene editing to larger tissues is likely to be more challenging owing to the difficulty of delivering the correct genomic modification to enough cells in the affected organ or tissue. Gene editing could be applied to gametes or embryos although within Europe the current regulatory environment (see next section) would appear to prohibit the translation of this approach. Conversely, pluripotent stem cell lines offer scientists a more accessible alternative to whole organism studies. They would allow genomic modifications to be verified at the cellular, nucleotide, chromosome and cellular level, enabling correctly modified cells to be selected and subsequently differentiated into desired cell lineages. In combination with other regenerative medicine technologies, including the potential for genetically modified animals and xenotransplantation, this could allow for gene-edited tissues for transplant and other more theoretical options such as living in vitro model neurological systems (Csobonyeiova et al 2015; Kimbrel and Lanza 2016). The development of gene editing is therefore closely linked with stem cell science, and regulation of one technology will therefore also affect the development of the other.

Governance and regulation in Europe

Stem cell research is governed by a number of European Directives which apply to different (though potentially overlapping) aspects of the translational pathway. Procurement and storage of primary human cells and tissues is governed by Directive 2004/23/EC, the 'Tissues and Cells Directive'. Subsequent development of stem cell based therapies as medicinal products is governed by Regulation (EC) No 1394/2007 on advanced therapy medicinal products (ATMPs). In combination these regulations set out the requirements for the traceability of all human biological material including the requirement that those traceability systems must allow 'reciprocal linkage' between original donor and end product (i.e. pseudonymisation).

Development of products classed as advanced therapy medicinal products or tissue engineered medicines (TEMs) are overseen by the Committee on Advanced Therapies within the European Medicines Agency (EMA) through the specific, centralised approval procedure for advanced therapy product candidates. Access to market then requires a successful Marketing Approval Authorisation from the EMA. In addition, any intellectual property protection for an ATMP in development is subject to the European Patent Convention (1973), the European Directive on the Legal Protection of Biotechnological Inventions (98/44/EU) and the rulings of the European Patent Office. The most relevant element in relation to human stem cells is still the Article 6(2)c of the Directive, which states that the use of human embryos for 'industrial or commercial' purposes should be excluded from patentability as this would be contrary to public order and morality.

Any clinical trials of a stem cell product carried out wholly or partially within a EU member state are subject to the EU Regulation on Clinical Trials (Regulation No. 536/2014). In addition, hospital exemption and named-patient access rules allow for some limited use of experimental therapies in human patients outside of formal clinical trials. Furthermore, sensitive personal data derived from stem cells is currently regulated by Directive 95/46/EC, soon to be replaced by the General Data Protection Regulation 2016/679. While the requirements set out in Regulations apply directly to all Member

States, those set out in Directives are subject to interpretation as they are transposed into the national legislation of EU counties. This allows for differences in regulatory requirements to persist between Member States, particularly regarding the use of hESC and iPSC for research.

For example, in relation to hESCs, EU countries that have signed and ratified the Oviedo Convention [43] for the most part have national legislation forbidding the creation of embryos for research purposes, whereas those countries yet to sign the Convention have taken more permissive approaches. In Germany, the derivation of embryonic stem cells is banned and the embryo is protected under the German Constitution (Grundgesetz) and the 1990 Law on the Protection of Embryos (Gesetz zum Schutz von Embryonen) [44]. However, embryonic stem cell lines can be imported specifically for research if the line was generated before a defined cut-off date, namely 1 May 2007 [45]. Similarly, France prohibits reproductive cloning and embryo creation for research purposes, and prohibits the use of human embryos and embryonic stem cells for research unless certain conditions are met [46]. Again, embryonic stem cells can be imported into France, subject to prior approval by the Agence de la Biomédicine [47]. In Italy the derivation of embryonic stem cell lines is also banned but it is permitted to use imported embryonic stem cell lines for research [48].

A more permissive approach to research using hESCs has been taken in the UK, Sweden and Belgium, who have not signed or ratified the Oviedo Convention. In the UK the Human Fertilisation and Embryology Act 1990 was amended (since amended by the Human Fertilisation and Embryology Act 2008) in 2001 to permit the destruction of embryos for hESC harvests but only if the research satisfies one of the following requirements: increases knowledge about the development of embryos; increases knowledge about serious disease; or enables any such knowledge to be applied in developing treatments for serious disease. Sweden forbids reproductive cloning, but allows therapeutic cloning [49] and authorized the creation of a national stem cell bank in 2002 [50]. In Belgium, the Law on Research on Embryos (2003) [51] and the Law on Medically Assisted Reproduction and the Destination of Supernumerary Embryos and Gametes (2007) [52] regulates research on embryos, as well as hESCs and lines. The Law on Research on Embryos permits research with surplus embryos provided six conditions are fulfilled, as set out in Art 3 [53]. Art. 4 of the Law on Research on Embryos prohibits the creation of in vitro embryos for the purpose of research, unless the needs of the research cannot be met with

43 ETS No.164 Convention for the protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine

44 § 2 (1) Gesetz zum Schutz von Embryonen 1990: http://www.aerzteblatt.de/download/files/2004/07/x0001251.pdf

45 §4 StZG Gesetz zur Sicherstellung des Embryonenschutzes im Zusammenhang mit Einfuhr und Verwendung menschlicher embryonaler Stammzellen (Stammzellgesetz – StZG): http://www.gesetze-im-internet.de/bundesrecht/stzg/gesamt.pdf

46 Law on Bioethics, LOI n° 2011-814 du 7 juillet 2011 relative à la bioéthique http://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000024323102&fastPos=2&fastReqId=823265692&categorieLien=cid&oldAction=rechTexte; Law on Bioethics, Law n. 2004-800 of 6 August 2004 (Loi n. 2004-800 du 6 Août 2004 relative à la bioéthique): http://ec.europa.eu/research/biosociety/pdf/french_law.pdfn:

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

47 Established by the Law on Bioethics, ibid.

48 The derivation of embryonic stem cell lines is banned but it is permitted to use imported embryonic stem cell lines for research: Law 40, 24 February 2004, Regulation of Medically Assisted Human Reproduction, Legge 24 Febbraio 2004, n. 40, Norme in materia di procreazione medicalmente assistita, G. U. N. 45

research with surplus embryos. hESCs can therefore be derived from surplus embryos following IVF or from embryos created for research in certain circumstances. Art 8 of the Law on Research on Embryos requires informed consent is given by donor(s) for the use of embryos for research purposes.

In contrast to hESCs, few countries have established specific legislation governing iPSCs. Some Member States instead regard iPSCs as any other human biological material and they therefore fall under relevant national legislative frameworks which permit their use. For example, in Germany, the commentary to §2 para.2 of the Stem Cell Law (StZG) specifically states that it is only applicable to hECS, therefore excluding iPSCs from its remit. Consequently iPSCs can be legally produced, used and imported into Germany [54]. In Belgium, the *Law on the collection and use of tissues and other human body parts for therapeutic and research purposes* (2008) [55] applies to human stem cells for therapeutic and research purposes, therefore including iPSCs. It covers activities in relation to procurement, collection, testing, processing, storage, distribution, and use (Art. 3). Donor consent must be obtained to use the tissue in order to derive iPSCs, as set out in Art 10. In the UK, human tissue that is stored with the intention of deriving iPSCs for research requires a research licence from the Human Tissue Authority (which regulates the collection storage and use of human tissue in the UK) as per s. 16 of the Human Tissue Act 2004 (HT Act; the Act extends to England and Wales, and Northern Ireland with a number of provisions also applying in Scotland. We do not distinguish these slight variations for the purposes of this analysis). However, once an iPS cell or line has been derived, it falls outside of the remit of the HT Act, and the storage of cell lines for research does not require an HTA licence. iPS cells or lines intended for use in human application are regulated by the Human Tissue (Quality and Safety for Human Application) Regulations 2007 (Q&S Regulations) and require a HTA licence.

The offering of stem cell products as a medical treatment comes under a different legal and regulatory regime to research. This is regulated by consumer law, the EMEA (more here). In this field the protections are consumer-orientated and very different to those imposed for research and the collection and storage of stem cells.

24-2-2004, at http://www.guritel.it/free-sum/ARTI/2004/02/24/sommario.html

49 The Swedish Code of Statues 1991:15 on Measures for Purposes of Research and Treatment Using Human Eggs (Lag 1991:115 om åtgärder i forsknings-eller behandlingssyfte med ägg från människa) as amended by the Swedish Code of Statutes 2006:351 on Genetic Integrity (Lag 2006:351 om genetisk integritet m.m.),

50 Biobanks in Medical Care Act 2002

51 Loi relative à la recherche sur les embryons in vitro 2003: http://www.ejustice.just.fgov.be/loi/loi.htm

52 Loi relative à la procréation médicalement assistée et à la destination des embryons surnuméraires et des gametes: http://www.ejustice.just.fgov.be/loi/loi.htm

53 These include that the research is intended for therapeutic purposes or is to generate knowledge in relation to fertility, sterility, organ or tissue transplantation or the prevention or treatment of diseases; it is based on the most recent scientific knowledge and complies with requirements of a correct scientific methodology; it is undertaken in a registered laboratory affiliated with a university programme for reproductive medicine or human genetics; it is undertaken under the supervision of a specialist doctor and by appropriately qualified persons; it is carried out on embryos up to fourteen days after fertilisation, excluding any time for cryopreservation; and there is no alternative research method that would be as effective.

54 Gesetz zur Sicherstellung des Embryonenschutzes im Zusammenhang mit Einfuhr und Verwendung menschlicher embryonaler Stammzellen (Stammzellgesetz – StZG): http://www.gesetze-im-internet.de/bundesrecht/stzg/gesamt.pdf

55 Loi relative à l'obtention et à l'utilisation de matériel corporel humain destiné à des applications médicales humaines ou à des fins de recherche scientifique: http://www.ejustice.just.fgov.be/loi/loi.htm

As illustrated, different jurisdictions have their own governance mechanisms in place, comprising of procedural requirements that need to be fulfilled. This can bethrough specific oversight bodies that are responsible for regulating stem cell research within the Member State. For example, in the UK, the two main bodies are the Human Fertilisation and Embryology Authority (HFEA), which is responsible for regulating research involving human embryos and the Human Tissue Authority (HTA), which regulates research involving human tissue in the UK. A HFEA research licence must be in place before an embryo can be used for the purpose of creating cell lines, as required by the Human Fertilisation and Embryology Act 1990 (as amended by the Human Fertilisation and Embryology Act 2008). A HFEA licence is not required however to conduct research on existing hESC lines that were originally derived from embryos. The HFEA's regulatory remit ceases when the derived hESC line has been fully characterised and cultured.

The HTA, which was established by the Human Tissue Act 2004, commences its regulatory authority at the point the embryo is disorganised and cells are grown to create cell lines with the intention that the lines may at some future time be used in human application. Any human tissue that is stored with the intention of deriving stem cells, whether hESCs or iPSCS for research requires an HTA research licence, as per s. 16 of the Human Tissue Act 2004 (HT Act). Furthermore, an establishment storing stem cell lines for human application may only do so under the authority of an HTA licence, as per reg. 7(1) of the Q&S Regulations. The storage of cell lines for research however does not require a HTA licence.

In Germany, the Robert Koch-Institut (RKI) is responsible for reviewing and approving import and research involving hESCs. Any research proposal with hESCs must be submitted to RKI in accordance with conditions set out in §5 StZG. The RKI grants authorisation once it has verified that the requirements for approval, as set out in §6 StZG, have been met and once approval has been obtained from a central ethics committee. If the proposal is approved, a fee is charged as per §2 StZG-KostV. In addition to regulatory approval, the RKI is also tasked with maintaining the register of scientific projects involving hESCs. Once again, in Belgium approval is required from a research ethics committee and the appropriate body, which is the Federal Committee for Medical and Scientific Research on Embryos In

Vitro (Commission fédérale pour la recherché médicale et scientifique sur les embryons in vitro). The Committee is tasked with giving the necessary authorization for such research, as set out in the 2003 Law on Research on Embryos.

Trends in global governance of stem cells

The diversity of legal instruments have also resulted in a disparate global and European regulatory system. The contemporary global landscape of stem cell regulation is characterised by three factors: increasing national regulatory diversity; persistent concerns about unproven stem cell treatments and so-called stem cell tourism; and expedited access pathways. All three issues are closely related. There has never been a single entirely harmonised global regulatory environment for regenerative medicine products (including stem cell therapies, gene therapies and combination products). The EMA and the US Food and Drug Administration (FDA) have many similarities, in the sense that regulatory assessment is based on comparable issues such as the degree of manipulation of cellular material. However the criteria for determining when and whether products fit into a particular classification are not identical. By way of illustration consider the distinction made by the FDA between '351' minimally manipulated homologous cell treatments and '361' more than manipulated / non-homologous products, and the EMA distinction between Advanced Therapy Medicinal Products which include any cell or gene therapy and Tissue Engineered Medicines (TEM) in which starting biological material is considered subject to substantial manipulation or where the product is 'not intended to be used for the same essential function or functions in the recipient as in the donor'. When other national regulatory frameworks are taken into consideration the differences are greater. Moreover, variations are not limited to technical criteria but include reimbursement pathways such as the conditional approval scheme recently introduced for regenerative medicine products in Japan which requires individual patients to pay up to 30% of costs of administering experimental treatments with the remaining costs covered by state insurance (Roseman et al 2016). Recent studies suggest that, despite the efforts of international collaborations like the International Society for Stem Cell Research (ISSCR), the International Consortium of Stem Cell Networks (ICSCN), and endeavours like EuroStemCell, the global regulatory environment for the translation of stem cell research is growing more fragmented (Roseman et al 2016; Sleeboom-Faulkner et al 2016).

At the same time the availability of stem cell treatments of unproven or uncertain therapeutic merit continues to be a major concern. Differences in national regulation allow patients who cannot access a particular treatment in their own country to travel to another jurisdiction where the intervention is available. In this regard unproven stem cell treatments constitute a small but growing segment of the global phenomenon described as 'medical tourism'. Exact numbers of users are hard to ascertain due to the somewhat covert nature of the practice, but Einsiedel and Adamson (2012) reported an estimated 700 clinics worldwide which they regarded as offering experimental stem cell treatments outside of a clinical trial setting. These practices raise concerns that patients will be harmed by what some commentators regard as "fraudulent, deceitful and inept practitioners of counterfeit and sham cellular therapies" (Caplan and Levine 2010: 25). Einsiedel and Adamson (2012) describe stem cell tourism destination as being mostly in developing counties. However, within the lifetime of the EU CelLEX project contested stem cell therapies have been an issue in many developed nations including Italy (Solarino et al 2015), Australia (Mclean et al 2015), and the USA (Knoepfler 2014; Lindvall and Hyun 2009).

The issue is further complicated by the fact that much of the regulatory divergence between nations described above is a result of different regulatory bodies developing their own local systems for expedited access to stem cell therapies. Most of these pathways, including those developed by the FDA and the EMA, allow for 'accelerated access' to stem cell products outside the traditional four-phase clinical trial structure (Roseman 2016). This makes it much harder to draw a clear distinction between legitimate medical innovation and exploitative practices based on traditional western medical criteria such as having a clear evidence base from clinical trials before an intervention can be offered (Lindvall and Hyun 2009). Sleeboom-Faulkner and colleagues (2016) caution that standards for research

In this regard unproven stem cell treatments constitute a small but growing segment of the global phenomenon described as 'medical tourism'.

conduct and ethics set by more cautious, well-resourced western laboratories threatens to exclude and devalue the work of researchers in less developed countries. This in turn can actively promote more regulatory diversity and fragmentation as national governments adapt global governance rules to meet local needs and situations and ensure that they are still able to develop new products and therapies for their own populations. This desire to adapt regulatory policy to sustain competitiveness in the stem cell field is not limited to countries like China or Argentina but is evident in Japan, Korea, the UK the USA and elsewhere.

Recommendations for improving the impact of current European regulation on translational stem cell science.

Assessment of the impact of current EU regulations and governance mechanisms on the utilisation and translation of human stem cells was based on reviews of the relevant academic and policy literature, workshops and discussions conducted during the lifetime of EU CelLEX, and surveys of key stakeholders in the regenerative medicine and stem cell science communities. The majority of respondents to the stakeholder surveys are based in public research institutions developing and using cell-based interventions whilst a small number of respondents have provided insights into commercialised use of cells for regenerative medicine use. Views were also canvassed from partners from the European Federation of Pharmaceutical Industries and Associations (EFPIA).

Access to cells and material

Respondents reported accessing material for developing ATMPs from a variety of sources including direct participant recruitment from Member States, from non-EU countries, through universities, hospitals and biobanks within the EU and from private institutions both within and outside Member States. The main issues related to obtaining material were the quality assurance of the material and the availability of accompanying data. Reduced costs and prompt delivery of material were also considered to be very important. In addition, respondents who attempted to share biomaterials were concerned

about legal issues in supplying human samples across borders and in maintaining quality and prompt delivery. In particular there appear to be some differences, even within Member States about what biosafety requirements are needed to move cells across borders.

Concerns about quality are likely to be assuaged when the various iPSC banks currently in development are fully operational. However, as noted above the value of iPSCs is greatly increased when information, including whole genome sequence data, about the tissue donor is also accessible by researchers. Some respondents expressed concern the General Data Protection Regulation might make sharing material and/or scientific collaboration across borders more difficult due to additional work required to interpret and meet its provisions, as well as the uncertainties about sharing with non-EU partners. The latter is particularly relevant as multinational collaborations and even multi-continental collaborations are becoming more common in stem cell research (Luo and Matthews 2013).

Recommendations

- **Governance frameworks should endeavour to enable as widespread a sharing of materials and data as possible for research purposes.**
- **Frameworks for sharing human tissue and cells need to be integrated with frameworks for sharing genomic information to facilitate human iPSC research on chronic diseases.**
- **Where the cells in question are part of a depletable resource, or where the cells include significant identifying information, an Access Committee should be established for each resource and ensure appropriate use of the material and data. Standards for such Access Committees should be harmonised.**
- **The uncertainty created by the current wording of the General Data Protection Regulation needs to be addressed and guidance created to ensure that users of cells in this context know how personal sensitive health data attached to cells can be processed.**
- **Cross-border standards in relation to the quality of cells need to be established with some urgency.**

Intellectual property rights

The majority of respondents collaborate with a small number of industrial/commercial organisations with a steady increase in commercial collaborations being measurable. The majority of respondents also collaborate with other public organisations for the purpose of exchanging information/methodologies. This confirms stem cell research as a highly collaborative field with strong industry ties. This is likely to increase with the promotion of public-private consortia in this area. At the same time it is important to realise that cell therapies are only one of several translational palthways for stem cell research and not necessarily the one in which major Euroean pharmaceutical companies are most heavily invested. A majority of respondents were also concerned with the impact of so-called ‘reach through rights' in biomaterials and related platform technologies and felt that the extent and power of these rights ought to be minimised, with the minority expressing indifference or disagreement. Traditional distinctions between public and private licensing terms may also become an issue as public-private collaborations and production of joint resources increases.

Recommendations

- **Clearer guidance needs to be established in relation to the pecuniary aspects of working with human cells and tissues. In particular, issues in relation to the commercialisation of cells need to be addressed in order to create legal certainty surrounding this difficult issue.**
- **This relates to cells for cell therapy but also other non-clinical applications.**
- **Care should be taken that the benefit of the exploitation of intellectual property is appropriately divided between public and commercial entities. This should be reflected in the relevant Material Transfer Agreement (MTA).**
- **Current communication channels between academia and commercial stakeholders seem to be sufficient and do not present an obstacle to the development of cell-based products and services.**

Gene editing

Gene-editing technology is closely related to stem cell and regenerative medicine technologies and is likely to be integrated into future products and applications. Owing to its associations with a number of high-profile areas that have proven to arouse public concern in the past including genetic modification of animals and plants, human germline gene editing and human enhancement, gene editing will likely become a significant governance issue in the near future.

- Many potential applications of gene editing are already covered by EU legislation. Therefore, human gene editing- specific legislation might not be warranted in Europe.
- Where GMO (genetically modified organism) governance frameworks in Europe are to apply to gene edited organisms, appropriate adjustments to the technical annexes of the Regulation ought to be considered.
- However, policy frameworks and governance mechanisms should comprehensively address their applications in the research and clinical contexts.
- Policy frameworks governing human germline editing should make explicit the scientific rationale and the underlying societal values in which they are supported.
- Owing to the degree of uncertainty still surrounding the individual and societal implications of such interventions, bona fide stakeholder engagement should precede the enactment of regulation governing their potential transition to the clinical context.

Current governance frameworks

Most respondents reported being quite familiar with the legal rules surrounding human cells. The majority are of the view that the current legislation was generally outdated and ambiguous. Moreover, global diversity of regulation of clinical translation adds to the difficulty for EU-based developers. In the case of iPSCs, there was a general feeling that the regulation was actually aimed at hESCs and had simply been poorly adapted. Workshop findings suggest that there is considerable diversity in legislation that applies to development and use of stem cell lines between member states, which is

thought to be a result of social concern rather than of the extent of research in this area. The main oversight over relevant activities is thought to lie with soft regulatory mechanisms, such as REC, institutional oversight, and the rules established by professional bodies.

Recommendations

- **There should be an effort to ensure that the governance frameworks are coherent and not conflicting; they should add to legal certainty not increase uncertainty.**
- **The discrepancy between observable/evidenced regulatory requirements and social concern about research/use in this area tought to be addressed.**
- **Where regulation clearly addresses social concern rather than empirical issues in the use of cells, this ought to be the subject of public debate.**
- **Policy scoping exercises should be aware not only of gene-editing but of a range of likely technological possibilities arising from the convergence of multiple platform technologies including 3D bioprinting and 3D cell culture, micro-fluidic 'organ on a chip' arrays, and whole genome sequencing.**
- **Stakeholder engagement should precede the enactment of regulation governing their potential transition to the clinical context.**
- **The EU is in a position to influence global regulatory norms by setting standards for good scientific ethical practice. However excessive stringency is likely to promote resistance and regulatory diversification among nations less able to meet these standards. At the same time global competition for innovation should not become a regulatory 'race to the bottom'. There is therefore a balance to be sought.**

One of the challenges of contemporary research is that it is increasingly global with periods of rapid change due to technological developments and innovation. In areas such as stem cell research, the law can only provide a framework that stipulates areas of prohibition and permissiveness based on societal expectations at a given point in time. Ideally it provides the oversight bodies and processes to guide further innovation and provide a framework for consultation, debate and deliberation. These frameworks must navigate the fine line between advancing innovation and commercial benefits for society, as well as managing risk and preventing harm while at the same time taking into account social expectations. The complexity of views around stem cell research is indicative of the difficulties of achieving this task. The challenge of regulatory appropriateness is compounded when innovation crosses defined boundaries such as the use of CRISPR-Cas9 technology in stem cell research or there are rapid advances such as the anticipated 3D bioprinting and 3D cell culture, micro-fluidic 'organ on a chip' arrays, and whole genome sequencing. In such cases a review of existing regulatory frameworks is required. Our review has shown that stakeholders in the field feel that the current legal framework is inadequate to meet the challenges of stem cell research, which is due to the global nature of research but also because of the range of regulatory approaches that have been taken across Europe and a regulatory framework that is unable to deal with the pace of innovation.

Regulatory frameworks and controls should be put in place within Europe, that would also help to set standards across the world. While there has been active development of norms and standards by the international scientific community these non-binding guidelines or statements of principle are not sufficient to prevent rogue or fraudulent practitioners particularly in regard to stem cell treatments. We suggest that attention needs to be given to the regulation of this field as part of a longer-term strategy. First steps that are urgently required are the integration of European frameworks for sharing human tissue and cells with frameworks for sharing genomic information to facilitate human iPSC research on chronic diseases and the clarification of the new General Data Protection Regulation in order to address how personal sensitive health data attached to cells can be processed. In addition, cross-border standards in relation to the quality of cells need to be established with some urgency. The benefits of a longer–term strategy for Europe regulation is that it would support global activity in this field and provide standards that would not result in a race to the bottom. The challenge is building consensus on how this might be done and engaging all stakeholders in the process.

References

Altshuler JS, Balogh E, Barker AD, Eck SL, Friend SH, Ginsburg GS, Herbst RS, Nass SJ, Streeter CM and Wagner JA, 'Opening Up to Precompetitive Collaboration.' (2010) 2(52) Science Translational Medicine DOI: 10.1126/scitranslmed.3001515

Belmonte JCI, Ellis J, Hochedlinger K and Yamanaka S, 'Induced pluripotent stem cells and reprogramming: seeing the science through the hype'. (2009) 10, Nature Reviews: Genetics, 878-883

Bubela T, Mishra A and Mathews D, 'Policies and practices to enhance multi-sectorial collaborations and commercialisation of regenerative medicine.' (2014) In Hogle LF (ed) Regenerative Medicine Ethics: Governing research and knowledge practices, 67-87. New York: Springer-Verlag.

Budin-Ljøsne I, Isaeva J, Knoppers BM, Tassé AM, Shen H-y, McCarthy M et al 'Data sharing in large research consortia: Experiences and recommendations from ENGAGE.' (2014) European Journal of Human Genetics 22; 317-321

Caplan A, Levine B Hope, 'Hype and Help: Ethically Assessing the Growing Market in Stem Cell Therapies' (2010) The American Journal of Bioethics, 10 (5) 24-25, DOI: 10.1080/15265161.2010.481980

Csobonyeiova M, Polak S, Koller J, and Danisovic L, 'Induced pluripotent stem cells and their implication for regenerative medicine.' (2014) Cell and Tissue Banking 16; 171-180

Cyranowski D, 'News: CRISPR gene editing tested in a person.' (2016) Nature 539; 479.

Das R, (2016) 'Five technologies that will disrupt healthcare by 2020.' Available at http://www.forbes.com/sites/reenitadas/2016/03/30/top-5-technologies-disrupting-healthcare-by-2020/#5758216f6252 Accessed 02/June/2016.

Einsiedel EF, Adamson H, 'Stem Cell Tourism and Future Stem Cell Tourists: Policy and Ethical Implications'. (2012) Developing World Bioethics 12(1) 35–44 doi:10.1111/j.1471-8847.2012.00319.x

Esch E, Bahinski A and Huh D, 'Organs-on-chips at the frontiers of drug discovery. Nature Reviews Drug Discovery' (2015) 14: 248-260.

French A, Suh, JY, Suh CY, Rubin L, Barker R, Bure K, Reeve R and Brindley DA. 'Global strategic partnerships in regenerative medicine.' (2014) Trends in Biotechnology 32 (9): 436-440.

Feng W, Dai Y, Mou L, Cooper DK, Shi D, Cai Z. 'The potential of the combination of CRISPR/Cas9 and pluripotent stem cells to provide human organs from chimaeric pigs'. (2015) International Journal of Molecular Sciences. 16(3): 6545-56

Gardner J, Faulkner A, Mahalatchimy A, and Webster A, 'Are there specific translational challenges in regenerative medicine? Lessons from other fields.' (2015) Regenerative Medicine 10(7): 885-895.

Goldman M, 'Public-private partnerships: New frontiers for collaborative research'. (2013) Science Translational Medicine, 5: DOI: 10.1126/scitranslmed.3007990

Hauskeller C, and Weber S, 'Framing pluripotency: iPS cells and the shaping of stem cell science.' (2011) New Genetics and Society 30 (4):415-431.

Heilker R, Traub S, Reinhardt P, Scholer HR, and Sterneckert J, 'iPS cell derived neuronal cells for drug discovery.' (2014) Trends in Pharmacological Sciences 35 (10): 510-519.

Hochfield W, Riffell J and Levinson N 'Four treatments that will transform healthcare in Europe in 2016.' (2016) European Pharmaceutical Review 21 (1):12-14.

Hu B-Y, Weick JP, Yu J, Ma L-X, Zhang X-Q, Thomson JA, and Zhanga S-C, 'Neural differentiation of human induced pluripotent stem cells follows developmental principles but with variable potency.' (2010) PNAS 107 (9) 4335-4340

Ilic D, 'iPSC in the past decade: the Japanese dominance.' (2016) Regenerative Medicine 11(8): 747-749.

Inoue H, Nagata N, Kurokawa H and Yamanaka S, 'iPS cells: a game changer for future medicine.' (2014) The EMBO Journal 33(5): 409-417.

Kimbrel EA and Lanza R, 'Current status of pluripotent stem cells: moving the first therapies to the clinic.' (2015) Nature Reviews Drug Discovery 14: 681-692

Kimbrel EA and Lanza R, 'Pluripotent stem cells: the last 10 years.' (2016) Regenerative Medicine 11(8): 831-847.

Knoepfler PS, 'From bench to FDA to bedside: US regulatory trends for new stem cell therapies' (2015) Advanced Drug Delivery Reviews 192–196 http://dx.doi.org/10.1016/j.addr.2014.12.001

Landecker H, 'Culturing life: How cells became technologies.' (2007) Cambridge, MA: Harvard University Press.

Liang P, Xu Y, Zhang X, Ding C, Huang R, Zhang Z, Lv J, Xie X, Chen Y, Li Y, et al. 'CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes.' (2015) Protein Cell. 6(5):363-72.

Lim MD, 'Consortium Sandbox: Building and Sharing Resources.' (2014) Science Translational Medicine 6 (242). Doi: 10.1126/scitranslmed.3009024.

Lindvall O, Hyun I, 'Medical Innovation Versus Stem Cell Tourism' (2009) Science 324 (5935) 1664-1665. doi: 10.1126/science.1171749

Luo J and Matthews KRW 'Globalisation of stem cell science: An examination of current and past collaborative research networks.' (2013) PLOS One 8 (9): e73598 DOI: 10.1371/journal.pone.0073598

Miao J, Guo D, Zhang J, Huang Q, Qin G, Zhang X, Wan J, Gu H, Qu L-J, 'Targeted mutagenesis in rice using CRISPR-Cas system.' (2013) Cell Res. 23(10):1233-6.

Mikami K, 'State-supported science and imaginary lock-in: The case of regenerative medicine in Japan.' (2014) Science as Culture 24 (2): 183-204.

McKernan R, and Watt FM, 'What is the point of large-scale collections of human induced pluripotent stem cells?' (2013) Nature Biotechnology no. 31 (10): 875-877.

McLean A, Stewart C, Kerridge I, 'Untested, unproven, and unethical: the promotion and provision of autologous stem cell therapies in Australia.' (2015) Stem Cell Research & Therapy, 6(33), 1-8

Morrison M, Klein C, Clemann N, Collier DA, Hardy J, Heiβerer B et al, 'StemBANCC: Governing access to material and data in a large stem cell research consortium.' (2015) Stem Cell Reviews and Reports 11; 681-687.

Muddyman D, Smee C, Griffin H, Kaye J and the UK10K Project, 'Implementing a successful data-management framework: the UK10K managed access model.' (2013) Genome Medicine 5:100 http://genomemedicine.com/content/5/11/100

Paull D, Sevilla A, Zhou H, Hahn AK, Kim H, Napolitano C, et al 'Automated, high-throughput derivation, characterisation and differentiation of induced pluripotent stem cells.' (2015) Nature Methods 12(9): 885-892.

Rao M 'Public Private Partnerships: A Marriage of Necessity.' (2013) Cell Stem Cell 12 (2):149-151.

Reardon S 'Gene-editing method tackles HIV in first clinical test.' (2014) Nature News and Comment. Available at http://www.nature.com/news/gene-editing-method-tackles-hiv-in-first-clinical-test-1.14813

Roseman A, Bortz G, Vasen F and Sleeboom-Faulkner M, 'Global regulatory developments for clinical stem cell research: diversification and challenges to collaborations.' (2016) Regenerative Medicine, E-publication ahead of print DOI: 10.2217/rme-2016-0072

Sleeboom-Faulkner M, Chekar CK, Faulkner A, Heitmayer C, Marouda M, Rosemann A, et al 'Comparing national home-keeping and the regulation of translational stem cell applications: An international perspective.' (2016) Social Science and Medicine 153; 240-249.

Solarino B, Laforgia M, Dell'Erba A, Laforgia N, 'Stem Cell therapy: medico-legal perspectives in Italy.' (2015) Frontiers in Cellular Neuroscience 9(240)

Suter-Dick L, Alves PM, Blaauboer BJ, Bremm K-D, Brito C, Coecke S, et al 'Stem cell-derived systems in toxicology assessment.' (2015) Stem Cells and Development 24 (11):1284-1296.

Takahashi K, and Yamanaka S, 'Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors.' (2006) Cell, 126: 663–676.

Takahashi K, Ohnuki M, Narita M, Ichisaka T, Tomoda K, Yamanaka S. 'Induction of pluripotent stem cells from adult human fibroblasts by defined factors.' (2007) Cell, 131:861–872.

Vaudano E, 'The innovative Medicines Initiative: A public private partnership model to foster drug discovery.' (2013) Computational and Structural Biotechnology Journal 6 (7): e201303017, http://dx.doi.org/10.5936/csbj.201303017

Webster A, and Eriksson L, 'Governance-by-standards in the field of stem cells: managing uncertainty in the world of "basic innovation".' (2008) New Genetics and Society, 27 (2):99-111.

Wiedemann PM, Simon J, Schicktanz S, Tannert C, 'The future of stem-cell research in Germany – A Delphi study.' (2004) EMBO Reports 5 (10):927-931.

Yu J, Vodyani MA, Smuga-Otto K, Antosiewicz-Bourget J, Frane JL, Tian S, Nie J, Jonsdottir GA, Ruotti V, Stewart R et al. 'Induced pluripotent stem cell lines derived from human somatic cells.' (2007) Science, 318: 1917–1920.

Zou Q, Wang X, Liu Y, Ouyang Z, Long H, Wei S, Xin J, Zhao B, Lai S, Shen J, et al. 'Generation of gene-target dogs using CRISPR/Cas9 system.' (2015) Journal of Molecular Cell Biology. 7(6):580-3. doi: 10.1093/jmcb/mjv061.

Umbilical Cord Blood Banking, Research and Clinical Applications

Report and Recommendations

Rosario Isasi
Bartha Knoppers
Pascal Borry
Mahsa Shabani
Herman Nys

3

The general objective of this WP4 was to examine and enhance the understanding and interpretation of national, regional and international legal and ethical issues surrounding umbilical cord blood (CB) research. This was envisioned as a critical and logical step towards building a robust implementation process for the ethical and legal frameworks governing cord blood research, banking and clinical applications in Europe, so as to harness its potential for novel therapeutic applications. The ultimate goal of this WP4 was therefore to provide policy recommendations to facilitate the interpretation and interoperability of the EU Tissues and Cells Directives, Recommendations and Resolution [56] in the context of CB research.

As a "Coordination and Support Action", the core objective of the EUCelLEX project was to provide recommendations to facilitate the use of stem cells in all aspects of the pipeline from research to healthcare. With the recommendations arising from this WP4, we hope to set forth the research agenda to further achieve this aim.

56 EU Member States of the Tissue and cells Directives (2004/23/EC, 2006/17/EC and 2006/86/EC, the Recommendation Rec (2004) 8 of the Committee of Ministers to member states on autologous cord blood banks, the European Parliament resolution of 11 September 2012 on voluntary and unpaid donation of tissues and cells (2011/2193(INI)) and the Opinion No.19 of the European Group on Ethics in Science and New Technologies to The European Commission on Ethical Aspects of Umbilical Cord Blood Banking (16 March 2004)

Using traditional methods of scholarship established in the social sciences, we collected, analysed and assessed data on the legal, ethical and social issues arising during the entire process of collecting, testing, banking and using cord blood in research and clinical applications. We focused on published literature pertinent to stem cells, cord blood cells and biobanking from the above mentioned subject areas. Documents were gathered through on-line and manual searches of databases such as PubMed, SSRN, LexisNexis, Westlaw, HeinOnline, and HumGen/StemGen as well through contact with our collaborators in order to identify additional literature.

We further conducted a critical, international, comparative analysis of policy focusing on laws, regulations and policies from regional, national, and international institutions and administrative bodies. Our study centered on a representative sample of EU member states countries involved in the EUcelLEX Consortium (Austria, Belgium, France, Germany, Hungary, Italy, Netherland and the UK) as well as a third country (Canada) to help describe the current policy framework for the donation, storage and use of human umbilical cord blood [57], [58].

Umbilical cord blood banking: dualism, policies and ethics

Today, umbilical cord blood is considered a prized source of multiple stem cells for both research and clinical applications. Demand for cord blood has exponentially increased. This is due to the fact that that while first regarded it as mere waste material it is now the source of treatments for a wide range of conditions (from hematologic diseases, to immune deficiencies and to genetic disorders) [59]. However, technical and scientific challenges from meeting the demands to generate a large volume of HLA diverse cord blood remain. Yet, research on cord blood cells offers hope for its use in novel therapies [60]. This together with is ability to generate pluripotent stem cells for regenerative medicine has further increased demand. Thus, not surprisingly, there is significant interest in banking such cells for both future allogeneic and autologous uses [61].

57 Pereira Beak C, Chargé SB, Isasi R, Knoppers BM. "Developing Educational Resources to Advance Umbilical Cord Blood Banking and Research: A Canadian Perspective". J Obstet Gynaecol Can. 2015 May; 37(5): 443-50.

58 Isasi R, Dalpe G, Knoppers BM. "Fostering Public Cord Blood Banking and Research in Canada". Stem Cells Dev. 2013 Dec; 22 Suppl 1:29-34. doi: 10.1089/scd.2013.0381.

59 Roura S., et. al. The role and potential of umbilical cord blood in an era of new therapies: a review. Stem Cell Research & Therapy (2015) 6:123.

60 Armson B.A., et. al. "Umbilical Cord Blood: Counselling, Collection and Banking". SOGC Clinical
Practice Guideline. JOGC (2015)328:832-844.

61 Rafi H., et. al. "Changing Trends of Unrelatedf Umbilical Cord Blood Transplantation for Hematologic Disases in Patients Older than Fifty Years: A Eurocord-Center for International Blood and Marrow Transplant Research Survey". (2016) Biol Blood Marrow Transplant 22:1717-1720.

Given the aforementioned developments, equitable access to ethically and legally sourced cord blood is of paramount importance. To address unmet medical needs, public CB banks aim to provide a reliable and quality source of HLA-diverse and quality controlled CB unites for both transplantation and research purposes. Yet, the co-existence of networks and institutions of both private and public, even of a hybrid commercial nature is an obstacle towards achieving these goals. Unsurprisingly, this typology is paired with heterogeneous socio-ethical and policy frameworks and diverse scientific practices. Moreover, certain ethical and policy issues arising in the research context are distinct from those arising during the process of collecting, donating and using CB for banking and clinical applications such as transplantation.

Policy Frameworks

Across Europe, there is significant heterogeneity in the policy approaches adopted for the collection, storage, use and distribution of CB cells. With the exception of Italy, European countries have refrained from enacting CB-specific legislation. The favored approach has been instead to regulate CB under general legislation that address a wide range of areas, such as norms dealing with quality, use and safety of human tissues (e.g. Austria, Belgium, Italy, United Kingdom, Canada and the Netherlands), medicinal products (e.g. Canada, Germany), transfusion and public health (e.g. France). Moreover, in most jurisdictions national policies and professional guidelines have been adopted from national (bio) ethics committees and medical societies (e.g. Austria, Belgium, Canada, France, Germany and United Kingdom) to set best practices for the field. Overall, policies encourage altruistic CB donation for allogeneic uses and storage in public banks. Critical attitudes prevail as concerns the alleged clinical potential of CB stored in private banks, and consequently, most guidelines recommended against private/commercial banking for autologous use.

The EU Tissues and Cell Directives and attendant Recommendations and Resolutions (“Directives”) do not specifically address private cord blood banks, but apply to them. In implementing the “Directives”, member states have attempted to strike a balance between relevant conflicting ethical principles, societal values and legal rights by either prohibiting commercial CB banks, or by strictly regulating the collection of CB for both allogeneic and autologous purposes.

The application of the “Directives” to CB cells rests in its legal classification. The Directives explicitly exclude blood and blood products from their remit, other than hematopoietic progenitor cells. At the national level, most countries do not expressively address the classification of cord blood cells in their legislation, overall they are widely treated as tissue (e.g. France, Canada, Belgium, etc.). The type of product or therapeutic approach selected during the product development process impacts what regulatory category applies, and, in turn, the requirements that must be adhered to [62]. Regulatory requirements for product classification determine the evidence needed for market entry, which in turn have significant effects over the thresholds for safety and efficacy, and hence could be factors either promoting or hindering innovation.

In addition, uncertainty over the legal status of CB brings to the fore questions surrounding control and dispositional authority over the CB and requires formulating regulatory responses. The debate is centered on who has dispositional authority over the CB, the mother or the child since it is biologically, developmentally and genetically part of the child. Responses to these questions and controversies must also be situated within the larger context of the general legal principle that the human body and its tissues are not legally ‘property’ and so cannot be owned. Thus, donation of other human materials (albeit with free donor consent) and the principle of altruism has long been an ethical and regulatory norm governing donation in Western countries. In the European context, where there can be no patrimonial rights in the human body or its parts, unless transformed into intellectual property (i.e. products, derivates, innovations).

Finally, in terms of the competent authority governing the collection, storage, use and distribution of CB; licensing, accreditation and oversight are carried out by a national health regulatory authorities, there is no specific agency for CB (e.g. Austrian Agency for Health and Safety, Belgium Federal Agency on Drugs and Health Products, Health Canada/Canadian Blood Services, Agence de la Biomedicine/ Reseau Francais de Sang Placentaire, Paul Erlich Institute, Italian Medicines Agency, Italian Cord Blood Network and Netherlands Health Care Inspectorate).

62 Isasi R., Charlebois K. “Uncertainty and Innovation: Assessing the Role of Cell-based Manufacturing Facilities in Shaping Regulatory and Commercialization Environments” (Submitted)

Policy Frameworks: specific recommendations

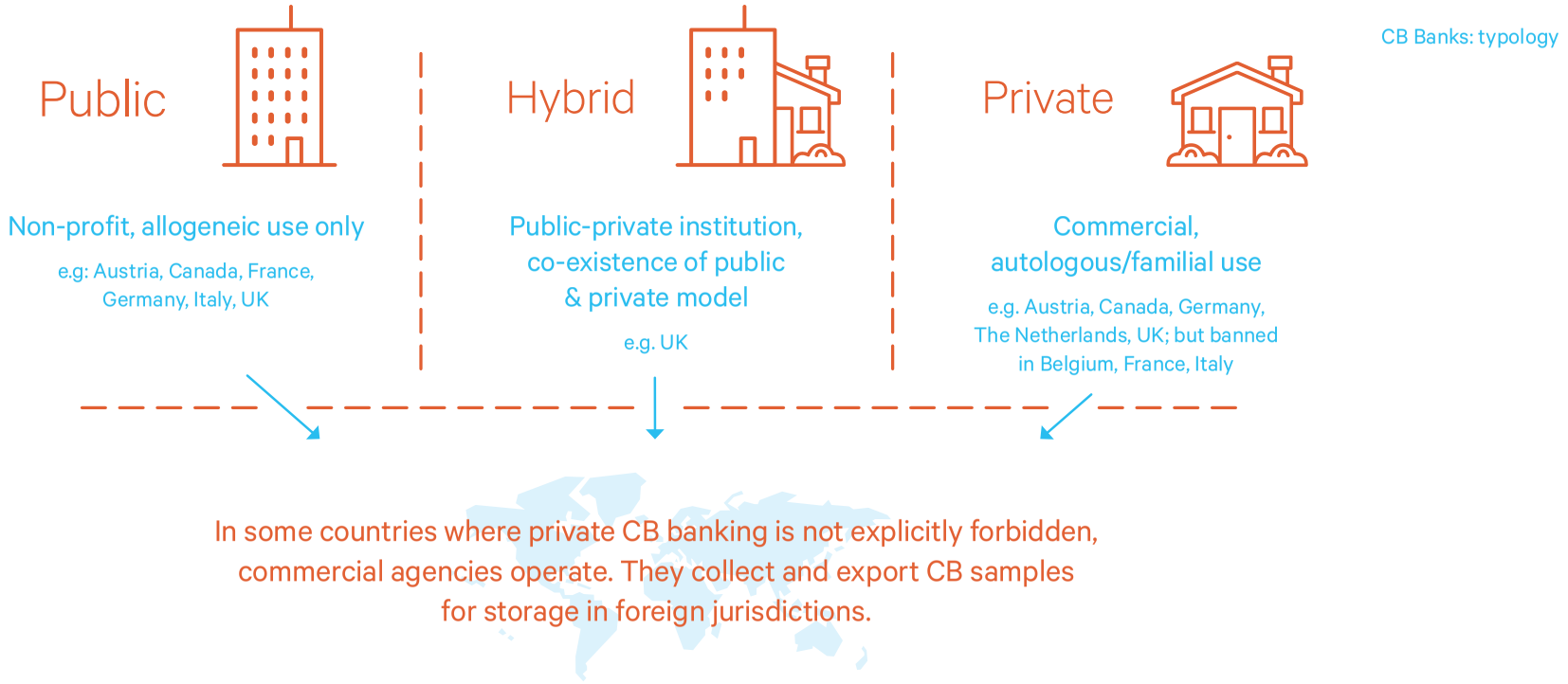
- **While CB-specific legislation might not be warranted in all jurisdictions, comprehensive policy frameworks addressing the collection, processing, testing, storage, use and (national-international) distribution of CB are needed.**
- **Policies should clearly determine how umbilical cord blood is classified; thereby defining its legal status.**
- **Policies should further clarify the conceptualization of custodianship and control of CB. This in turn, would elucidate the concomitant stakeholders' rights, obligations liabilities (i.e. parents, children, biobanks, researchers etc.)**
- **Normative frameworks should address the governance mechanisms for research use of CB whether sourced from national, private or hybrid CB banks.**

The Duality of Public Networks and Commercial Cord Blood Banks

While a public CB Bank is established to collect indirect donations and directed donations in high risk families for allogenic purposes, parents also have options in some Member States to store their child's CB in a private biobank mainly for autologous or family use. While the ethical concerns of cord blood banking in the case of donated samples for the purposes of allogeneic transplantation or research are the same as for any tissue bank (EGE Opinion 19, 2004), CB banking for potential future autologous uses raises additional ethical concerns. There is a need to strike a balance between the values in conflict mainly, the value of freedom and free enterprise versus respecting the principle of justice and solidarity in which access to healthcare should be on an equitable basis and based on realistic needs. Directive 2004/23 does not specifically mention commercial or for-profit cord blood banks but also applies to them. According to article 12 'MS shall take the necessary measures to encourage voluntary and unpaid donation of human tissues and cells with a view to ensuring that, insofar as possible they are obtained from such donations.'

The legal (and ethical) acceptability of commercial/private and hybrid (i.e. public-private) CB banks varies across Europe. In implementing the Directive, some member states have opted for prohibiting entirely commercial CB Banks, while others have strictly regulated the collection, storage and use of CB for autologous or allogeneic potential future purposes (e.g. Belgium). In view of this polarization of views and approaches, it is critical to understand stakeholders' perceptions, desires and preferences. This is crucial if the latter is to be used as justification for policy action. It is also essential to effectively respond to societal needs and concerns.

CB Banks: typology



In view of this polarization of views and approaches, it is critical to understand stakeholders' perceptions

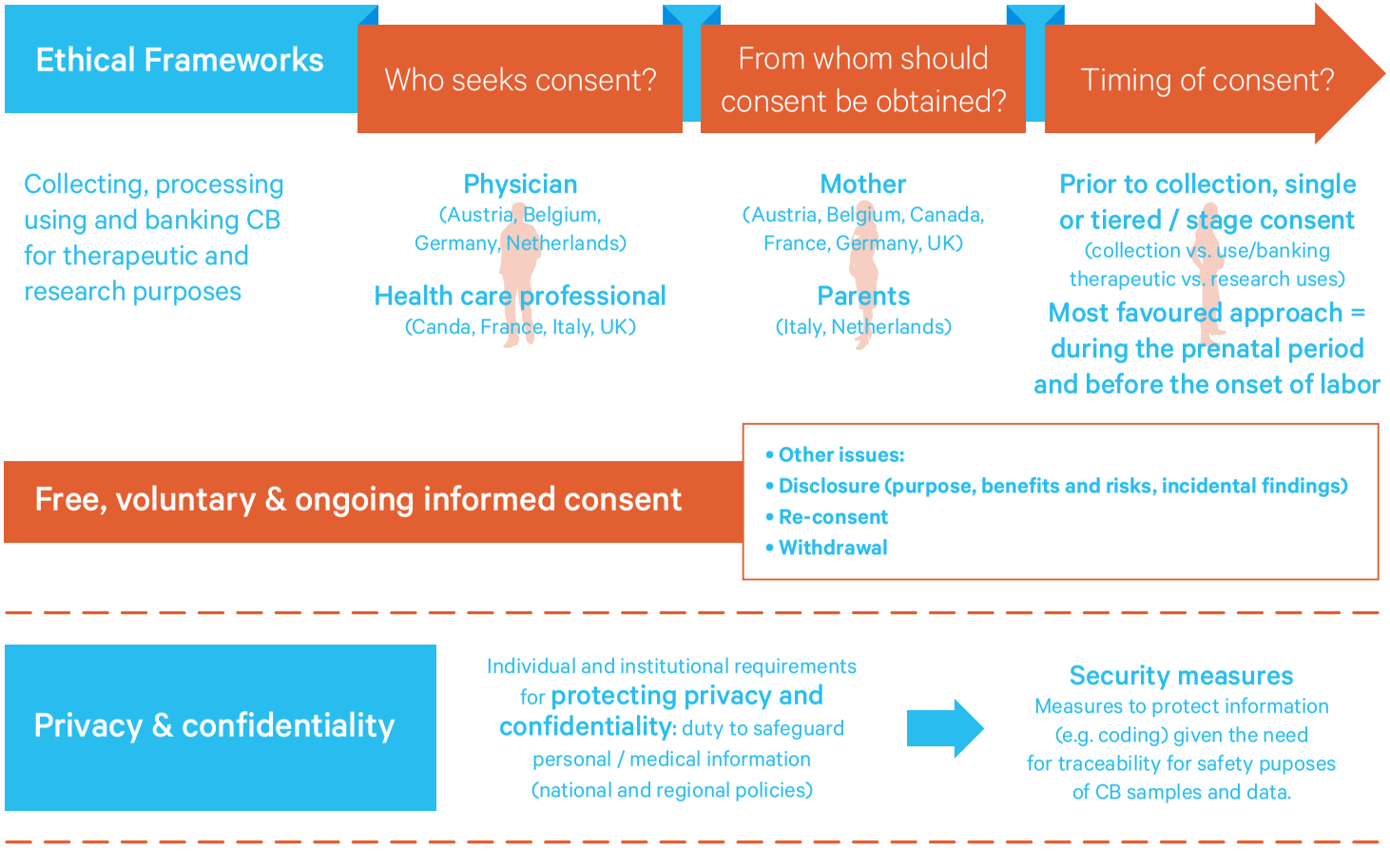
The duality of public networks and commercial cord blood banks: specific recommendations

- Across Europe, there is a need for empirical studies gathering societal attitudes towards CB donation, banking and prospective uses (i.e. allogeneic and autologous clinical purposes, research). To help inform policy approaches, the preferences and needs of both prospective donors and receipts (as well as of families with known risks of disease), should be better understood. The (co)existence (or not) of public, private and/or hybrid CB banks in a given country should be transparent and meet public needs.
- In jurisdictions where private/commercial CB banks are prohibited or restricted, legal loopholes allowing for the operation of commercial CB agencies, collecting and exporting CB samples for storage in foreign jurisdictions in order to avoid such restrictions should be addressed.
- MS should address the need for raising public awareness over the utility and application of CB for clinical and research uses. It should promote CB donation through tailored educational materials directed at the public in general, and prospective parents as well as physicians/health care workers in particular.

Ethical Frameworks

Given the absence of CB-specific policies, in most jurisdictions protection for patients' rights and research participants is governed by provisions relating to the general rules for research participants and for donors of tissue and reproductive materials. By virtue of national and regional policies, there is a level convergence in approaches towards core ethical principles, such as respect for autonomy (informed consent, avoidance of conflict of interest between the health care team and the research or CB banking teams), respect for privacy and confidentiality (i.e. protections for donor identity given the potential traceability of CB cells), non-commercialization of human biological materials. However, clarification over the application of such core ethical principles to the specific context of CB is still needed.

CB donation and banking pose vexing questions given that the CB contains sensitive private information related to the child, which raises questions regarding measures to protect privacy and confidentiality. What are the implications of genetic testing of CB for the informed consent process? Should donors be informed of test results? Additional vexing questions pertain to: (1) whether testing should not be performed if there is no direct and immediate benefit for the child; (2) who should have authority over secondary uses of the stored CB when the child reaches legal age, (3) Should the child be re-contacted or re-consented? It is of special interest with regard to respecting genetic privacy of the child and maintaining confidentiality of the data. Any future rights of the child over CB are not clear and yet to be investigated.



Ethical Frameworks: specific recommendations

- Policies should clearly outline the professional responsibilities emerging during the different stages of collecting, processing, testing, using and distributing CB units. Such policies should distill, when warranted, between the clinical and the research contexts•In jurisdictions where private/commercial CB banks are prohibited or restricted, legal loopholes allowing for the operation of commercial CB agencies, collecting and exporting CB samples for storage in foreign jurisdictions in order to avoid such restrictions should be addressed.
- Guidance with respect to requirements for obtaining prospective informed consent during the different phases of CB collection, testing, storage, use and distribution are needed. In particular, policies should clearly articulate: (i) requirements for obtaining parental, maternal, or a joint parental-maternal consent; individual responsible for seeking consent (i.e. physician, health care professional), (iii) timing for obtaining consent (i.e. prior to the collection, during prenatal period, before onset labor), (iv) types of consent (i.e. single, tiered or staged consent).
- Scientific advances such as the potential to immortalize CB by the derivation of pluripotent stem cell lines, together with the capacity for long-term storage of CB and its derivates; calls for guidance with respect to whether there is an ethical imperative to obtain informed consent from the child when he/she reaches adulthood.
- Policies should prospectively address the mechanisms and safeguards for the international distribution of CB cells and associated data for both clinical and research purposes, together with mechanisms for donor withdrawal.
- Given that CB cells contain medical and genetic information associated with the donors (mother, child) CB banks, regardless of its nature, should establish and make publicly available the policies and procedures in place to safeguard donors' privacy and confidentiality.

Respecting Participants' Interests

Once biological samples has been collected from individuals for the purpose of establishing biobanks and cord blood banks and multiple research purposes, it is imperative to respect the wishes of the individuals. Public and research participants' perspectives toward sample and data sharing should be sought and adequately addressed in the course of governing sample and data sharing. Individuals understand the potential benefits accrued via sample and data sharing while remaining wary of the potential concerns that might endanger their personal rights or social benefits. Nevertheless, they favor sample and genomic data sharing when they believe benefits outweigh potential risks. The consent mechanism addresses a number of concerns of the public and research participants in the context of genomic data sharing, including representing a sign of respect and a mechanism to maintain control on data. In order to get better understanding of the concerns of general public, through a systematic literature review study, we collected the attitudes and opinions of the research participants and general public towards biological sample and data sharing for research purposes and in the context of biobanking. We provide the following recommendations on the basis of this study [63], [64], [65].

Respecting Participants' Interests: specific recommendations

- **Key concepts such as privacy are construed in heterogeneous ways amongst the public, necessitating a tailored approach to be adopted to protect privacy in the face of sample and data sharing.**
- **Research participants and the public are concerned about the breadth of sample and access, as well as subsequent research purposes, suggesting de-identification of data may not resolve all the research participants' concerns.**
- **Implementing robust oversight mechanisms and introducing higher transparency into the sample and data sharing policies by institutions will build an atmosphere conducive to building trust among the public and research participants.**

63 Shabani, M., Bezuidenhout, L., Borry, P. (2014). Attitudes of research participants and the general public towards genomic data sharing: a systematic literature review. Expert Review of Molecular Diagnostics, 14 (8), 1053-1065.

64 Schneider D., et. al. "Accelerating the Development and Validation of New-Value-Based Diagnostics by Leveraging Biobanks". Public Health Genomics (2016) 19:160-169.

65 Weisbrot D. "The ethical, legal and social implications of umbilical cord banking: Learning important lessons from the protection of genetic information'. JLM (2012) 19:525-549.

Ethics Oversight

In order to address the ethical and legal concerns that are associated with the collection, storage, use and sharing of biological samples and data including cord blood, establishing adequate governance mechanisms is required. There are some traditional governance instruments such as oversight by ethics committees on the proposed research proposals. However, biobanking and the wide range of downstream sample and data uses pronounced a need for utilizing novel tools and instruments. Such oversight tools should enable an ongoing oversight on uses of samples and data. We investigated one of these novel instruments, namely data access committees and provided recommendations on this matter [66], [67]:

Ethics Oversight: specific recommendations

- **Harmonization of sample and data access arrangements is necessary for successful international sample and data sharing and to ensure fairness of the procedure.**
- **To avoid redundancies, the relationship between data access committees and other oversight bodies such as ethics committees and the scope of their oversight should be clarified.**
- **Oversight mechanisms on the enforcement of sample and data access agreements and standards should be elaborated and arrangements made for detection and sanction of violations.**

Commercialization

In the recent years, some population biobanks are involved in various commercial collaborations. It has been argued that commercial involvement would be beneficial for population biobanks in terms of long-term maintenance and product development. The commercial involvement in research biobanks has raised a number of ethical concerns to date. Research participants and general public may have misgivings concerning commercial involvement in biobanks. It is necessary to ensure the interests of public and private parties have been reconciled, when such partnerships are planned [68], [69]. Thereby, the potential concerns about adverse impact of commercial involvements on the public trust will be addressed. In addition, commercial involvement could exacerbate privacy issues and consequently

66 Shabani, M., Knoppers, B., Borry, P. (2015). From the principles of genomic data sharing to the practices of data access committees. EMBO Molecular Medicine, 7 (4), art.nr. 10.15252/emmm.201405002, 1-3.

67 Shabani, M., Knoppers, B., Borry, P. (2016). Genomic Databases, Access Review, and Data Access Committees. In: Kumar D., Antonarakis S. (Eds.), Medical and Health Genomics Elsevier, 29-36.

68 Caulfield, T., Burningham, S., Joly, Y., Master, Z., Shabani, M., Borry, P., Becker, A., Burgess, M., Calder, K., Critchley, C., Edwards, K., Fullerton, S., Gottweis, H., Hyde-Lay, R., Illes, J., Isasi, R., Kato, K., Kaye, J., Knoppers, B., Lynch, J., McGuire, A., Meslin, E., Nicol, D., O'Doherty, K., Ogbogu, U., Otlowski, M., Pullman, D., Ries, N., Scott, C.,Sears, M., Wallace, H., Zawati, M. (2014). A review of the key issues associated with the commercialization of biobanks. Journal of Law and the Biosciences, 1 (1), 94-110.

69 Knoppers et al. (2016). "Attaining Majority in Research: Re-contact for Consent to Continued Participation?". IRB. In press.

underline the possible requirement for additional oversight or mechanisms to protect participants' privacy. We discussed the issue in the recent policy papers and provided recommendations:

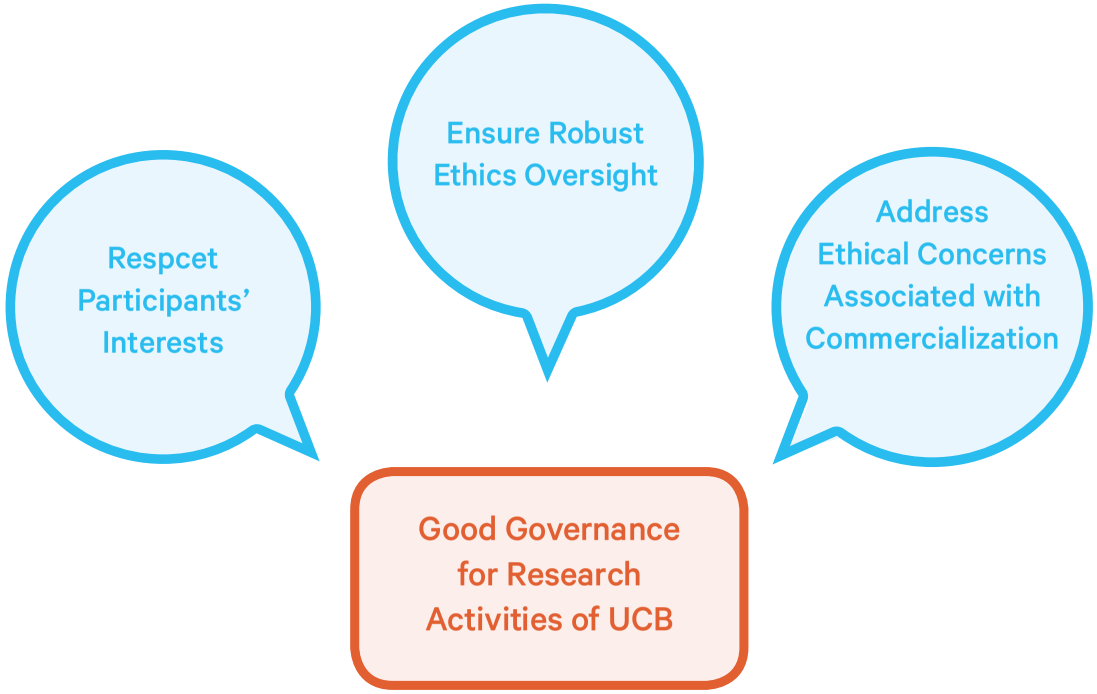
Commercialization: specific recommendations

- **Consent challenges, such as the possible requirement to obtain permission to re-contact or the need for re-consent should be taken into considerations from the beginning. The challenges of consent and re-contact could be intensified when samples and data are collected in the pediatric setting.**
- **Challenges for oversight bodies, such as research ethics boards, in monitoring downstream commercial research should be addressed by adopting adequate governance mechanisms.**
- **Possible tensions regarding the ownership and sharing of biological samples and data are expected to arise from commercial involvements. Adequate legal safeguards therefore need to be in place in order to protect the rights and interest of the involved parties.**
- **Uncertainty concerning the use and control of the resource if biobanks go bankrupt or lose funding support should be considered when developing partnership plans.**

Good Governance for Research Activities of UCB

In general, the lessons learned from the biobanking and data sharing could provide important insights for governance of research activities of UCB in an ethical and responsible fashion. In summary, governance of storage, use and sharing of CB for downstream research purposes should be attentive to the concerns of the individuals. In particular, adequate information should be provided to the parents (and when it is necessary to the child) concerning the scope of the research, the rights of the involved parties and the existing legal and ethical safeguards. In order to ensure the ethical underpinning of the research governance in the framework of UCB, adopting effective oversight mechanisms is imperative. In the recent years, increasing attention has been paid to the oversight of collection and sharing of biological samples and genomic data for research purposes. It has been suggested that the traditional approaches to oversight of research should be updates and when it is necessary the existing oversight

bodies to be equipped with adequate tools and mechanisms in order to be able to address the emerging ethical and legal concerns. We recommend that a similar approach should be taken in establishing adequate oversight on research activities of UCB. In doing so, it is particularly important to develop fair storage, sharing and use arrangements and communicate it to the public. This will foster transparency in governance of research activities of UCB and consequently maintain public trust.



In order to ensure the ethical underpinning of the research governance in the framework of UCB, adopting effective oversight mechanisms is imperative.

Research Activities of UCB: specific recommendations

- Adequate governance mechanisms should be adopted in order to ensure ethical and legal underpinnings of the research activities of UCB. In particular, fair storage, use and sharing arrangements should be developed by the UCB and communicated to the public.
- Concerns of the parents and the general public in terms of the scope of the research activities of the UCB should be adequately addressed. For research activities of the UCB, it is necessary to inform parents about the withdrawal options. Consent for the research should be clear and not to be conflated with the other activities of the UCB. Policies regarding arrangements for re-contacting children when they attain majority (when necessary) should be prepared.
- In the view of commercialization of UCB, adequate safeguards for privacy of individuals should be provided. The concerns of the general public about commercialization of biobanks in general, particularly in terms of ultimate benefits for the public should be respected.

Translational research

Report and Recommendations

Lisa Oberauner-Wappis *
Kurt Zatloukal *
Georges Dagher **

* Medical University of Graz. ** Inserm, Paris France.

4

The main focus of work package 5 was to analyse current legislation concerning the therapeutic use of somatic cells, in both the public and private sectors and in a number of European countries. Hence, the project objectives were to assess the relevance of current European legislation in order to provide the data needed to establish a European framework for the use of stem cells of every type (embryo, adult and IPS cells from cord blood) in the light of recent scientific, legal and institutional developments in Europe.

Few scientific advances have been met with as much enthusiasm as has the development of human embryonic stem cells and induced pluripotent stem cells (hESC and iPSC). During the past decade, they have constituted the greatest promise for the treatment of degenerative diseases. With the availability of human pluripotent stem cells (hPSCs) and greatly improved protocols for their directed differentiation, this prospect could become a reality for several disease-relevant cell types. Recent advances in the stem cell field indicate that the directed differentiation process could indeed translate into effective therapies for currently intractable disorders (Kriks S et al., 2011 ; Shiba Y et al., 2012 ; Sundberg M et al., 2013 ; Wang S, et al., 2013). In parallel to this breakthrough, research is on-going to assess lineage, fate and function of stem cells derived cell types as well as novel technologies for translation into humans. In the past few years there has been a strong drive towards translating cell therapy research into the clinic. Two of the

key elements for any successful translational application are the ability to produce hPSC-derivatives in a scalable and GMP-compliant manner and crucially, the selection of appropriate disease targets. Implementing hPSC-based approaches will in regenerative medicine will require multidisciplinary teams of clinicians and scientists with expertise in directed differentiation, GMP production, large animal studies, tissue engineering as well as ethicist and patient advocates. In addition, navigating the complex EU regulations requires specific expertise in both law and science as the frontier between research and clinic fades away in the pioneering clinical approaches. Indeed, the translational pipeline from basic research to the delivery of innovative stem-cell based therapies is covered by a variety of European legal instruments ranging from regulations on marketing authorization to directives and legislation about, basic stem cell research, clinical trials, genetic data, safety, intellectual property and guidelines of good clinical practice. Implementation of these directives in EU member states (MS) led to a heterogeneous legal landscape thus hampering the development of hPSC and iPSC clinical applications (Migliaccio G et al., 2013 ; McBlane JW., 2015).

The role of WP5 in EUcelLEX

There are a number of factors that have limited translational transfer from basic research to clinical and economical applications. Among these there is a need for transnational access conditions and of translating culture protocols developed in research laboratories into clinically applicable manufacturing designs.

In order to meet these needs, the main focus was (1) to identify practical roadblocks at the intersection between therapy and research, (2) to analyse the practical roadblocks at the intersection between therapy and research, (3) to enable stakeholder engagement (e.g. IMI, ECRIN, BBMRI) and (4) to assess EU legislation pertinent to the use of stem cells in toxicological assessment.

Towards that aim, the process of stem cell research, therapy and translation from research to therapy was modelled to pinpoint and clearly present potential roadblocks within the heterogeneity of MS legislation to specific steps. An event-driven process chain (EPC) was chosen (Signavio Process Editor collaborative platform), where three cooperation partners evaluated and modified the EPC according to their expertise and scientific background. They identified (i) existing concrete processes and procedures implementing the different directives for research and therapy, (ii) process differences/ similarities and (iii) gaps left by directives especially transnational and specific informed consent.

Translation Processes

To identify and analyse roadblock as well as to enable active stakeholder engagement the idea arose to apply a process oriented approach instead of classical collections of lists. The process concentrates on an aggregation level to show best for which activity which regulations, legislations and directives apply. Therefore, the technical platform chosen to describe the process was Signavio, a professional, collaborative process design platform which is free for academic use and publication as in our case for the EUCelLEX project.

The technical platform Signavio is a professional, collaborative process design platform which is free for academic use and publication as in our case for the EUCelLEX project. A full description of all possible technical features in using the Platform is available at (https://www.eucellex.eu/wpcontent/uploads/2014/07/SignavioProcessEditor.pdf). The system aims at collecting various information on the relevant legislations applying to stem cells. All partners have been granted access to the tool in order to complete it for their own country.

To help harmonising the EU regulation in this field we have depicted the processes of research and those of therapy and highlighted their interactions. This helps identifying the differences and similarities between the two pathways. There are four different processes for the use of autologous or allogenic cells for patients as depicted in Figure 1. Three of them relates to cells used for therapy. Process 4 concerns cells used for research

- **Process 1** is a direct use of cells, following agreement issued from competent authorities. This is covered by the cell and tissue directive 2004 and 2006 that is presently in revision. This process requires also an analysis of risks as well as the informed consent of the patient

- **Process 2** is the most complex one as it concerns the use of Induced Pluripotent Stem Cells (IPSC), Umbilical Stem cells (USCs), Umbilical Cord blood cells (UCBs). It also involves substantial handling and transformation of the cells as well as multiplication of the number of cells. This is covered by the tissue handling regulations as well as biobank and appropriate transport standards. It requires the informed consent of the patient.

- **Process 3** concerns the use of Embryonic Stem cells. It is covered by countries specific regulation as well as tissue handling regulations, and appropriate transport standards. It requires the informed consent of the patient. Process 3 have similar features as process 2 in relation to a) the agreement of competent authorities, b) finding the cell provider c) transport of cells.

- **Process 4** concerns cells used for research. It is covered by tissue regulation, transport and biosafety regulations. It also requires agreement for clinical trial from the research entity, internal review board and ethical committee as well as patients informed consent.

All the four processes, share the same steps in terms of transformation prior to their application in patient monitoring of patients and reporting adverse effects. These steps require Good Manufacturing Practice, biosafety regulation and reporting regulations.

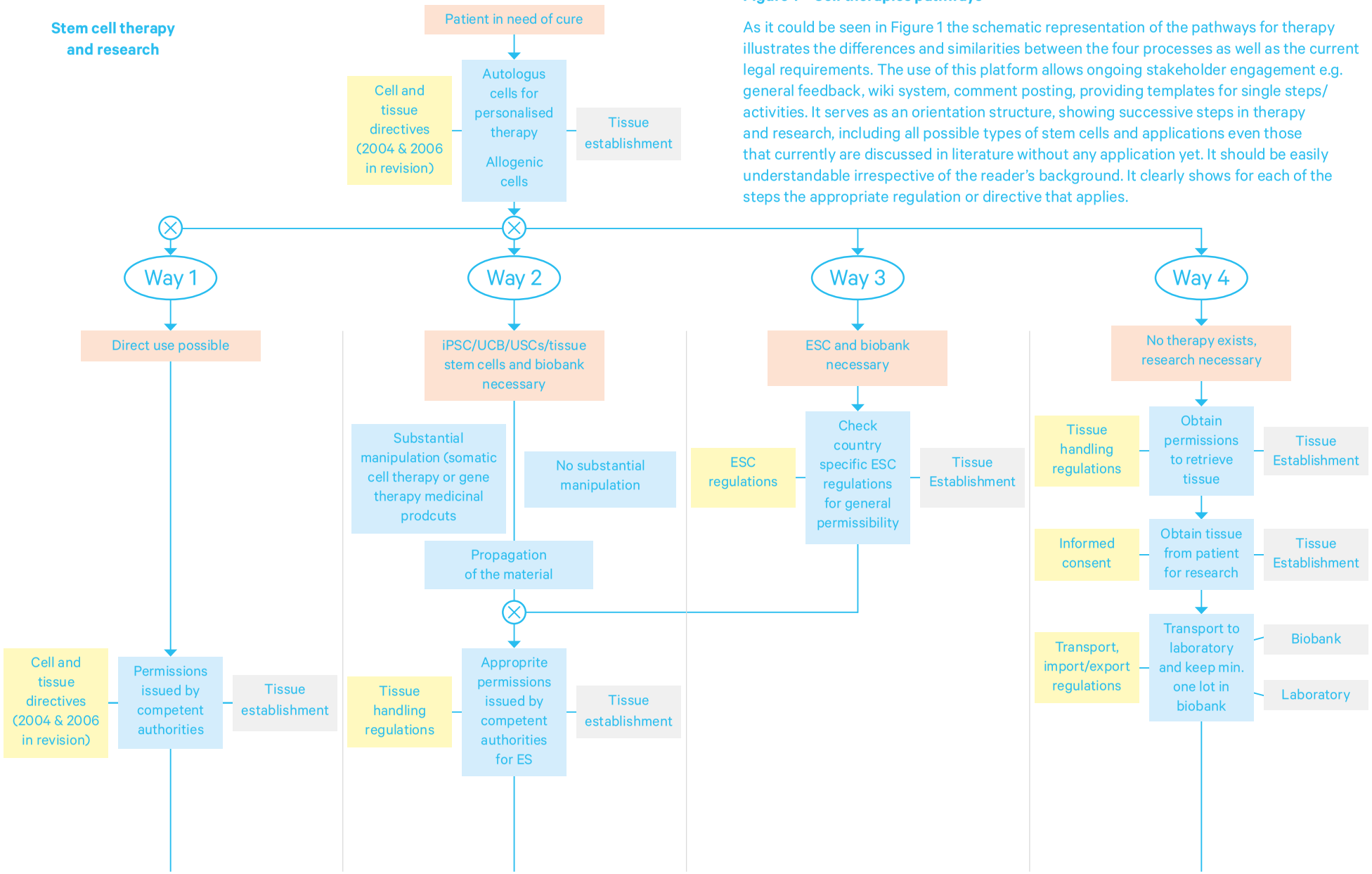
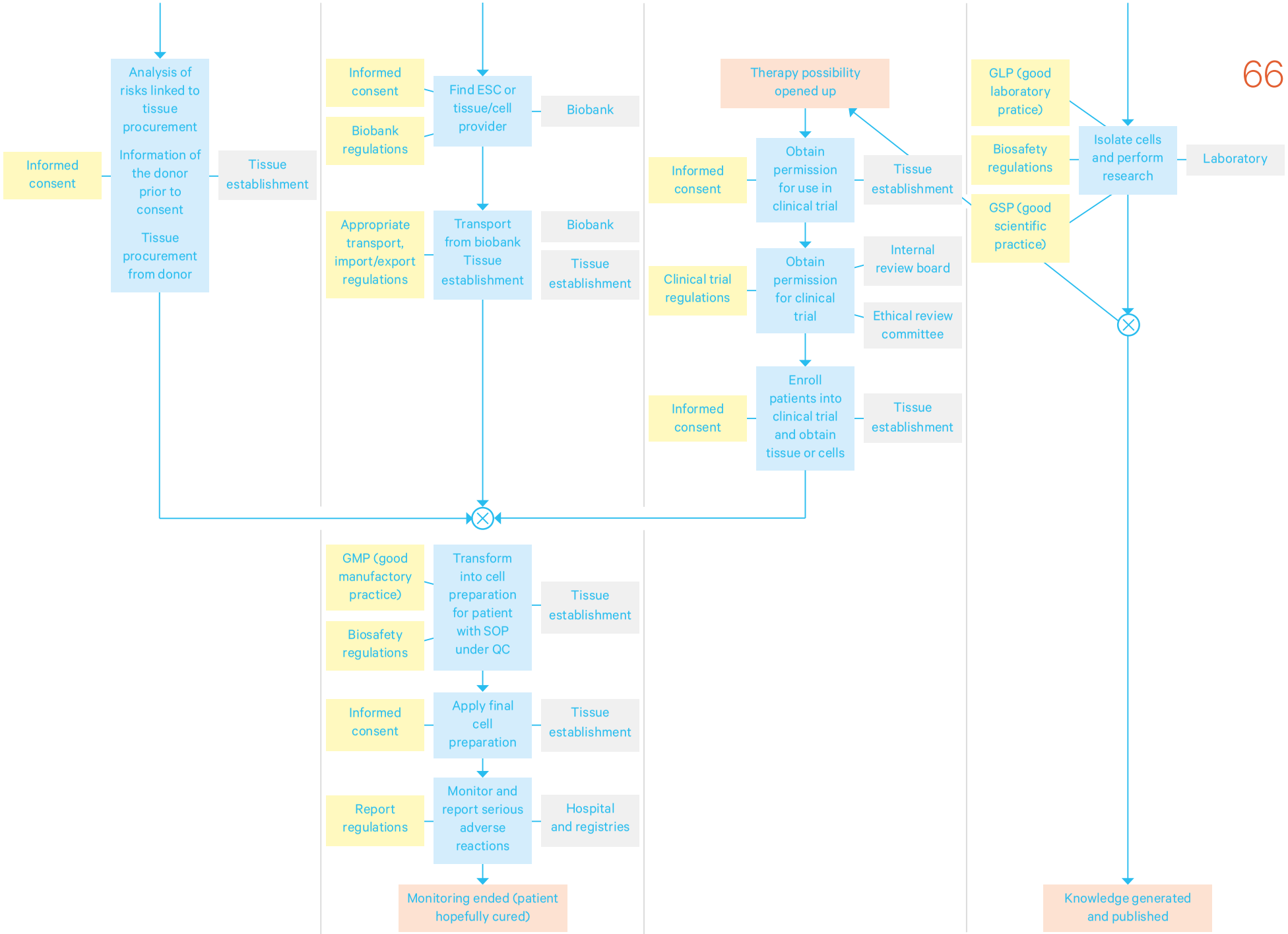


Figure 1 – Cell therapies pathways

As it could be seen in Figure 1 the schematic representation of the pathways for therapy illustrates the differences and similarities between the four processes as well as the current legal requirements. The use of this platform allows ongoing stakeholder engagement e.g. general feedback, wiki system, comment posting, providing templates for single steps/ activities. It serves as an orientation structure, showing successive steps in therapy and research, including all possible types of stem cells and applications even those that currently are discussed in literature without any application yet. It should be easily understandable irrespective of the reader's background. It clearly shows for each of the steps the appropriate regulation or directive that applies.


Analysis of risks linked to tissue procurement
Information of the donor prior to consent
Tissue procurement from donor
Informed consent
Tissue establishment
Informed consent
Biobank regulations
Find ESC or tissue/cell provider
Biobank
Appropriate transport, import/export regulations
Transport from biobank Tissue establishment
Biobank
Tissue establishment
Therapy possibility opened up
Informed consent
Obtain permission for use in clinical trial
Tissue establishment
Clinical trial regulations
Obtain permission for clinical trial
Internal review board
Ethical review committee
Informed consent
Enroll patients into clinical trial and obtain tissue or cells
Tissue establishment
GLP (good laboratory pratice)
Biosafety regulations
GSP (good scientific practice)
Isolate cells and perform research
Laboratory
GMP (good manufactory practice)
Biosafety regulations
Transform into cell preparation for patient with SOP under QC
Tissue establishment
Informed consent
Apply final cell preparation
Tissue establishment
Report regulations
Monitor and report serious adverse reactions
Hospital and registries
Monitoring ended (patient hopefully cured)
Knowledge generated and published

Ethical concerns linked to stem cell research

At the 13th world congress of bioethics hosted by the International Association of Bioethics (IAB) in Edinburgh on Tuesday 14 June 2016, we organized a satellite meeting where **Stem cell Research Scientists met Ethicists**. Three speakers were invited Prof. Christian Chabannon, Prof. James A. Adjaye and Prof. Peter Schlenke to give a talk on possible ethical questions related to stem cell research.

1. Prof. Dr. Christian Chabannon: "Human Stem Cell Banking & Therapeutics" [70]

Human stem cell banking and therapeutics where cellular therapies hold great promises in the field of regenerative medicine and immunotherapy of various chronic diseases including cancers. Modern forms of cellular therapies stem from the medical practices of organ, tissue and cell transplantation. Complex and sophisticated engineering of the original biological material – potentially involving genetic manipulation of the cells through various means - will increasingly involve central and industry-operated manufacturing facilities as alternatives to scattered academic cell processing facilities that ensure non substantial manipulations needed for cell transplantation. European regulators have already defined a new category of medicinal products denominated "Advanced Therapy Medicinal Products" or ATMPs that include somatic cell therapy products, gene therapy products and products of tissue engineering; regulatory requirements for the manufacturing of ATMPs differ of regulatory requirements for processing cell transplants. Nevertheless, since most cellular therapies in development use primary human cells or tissues rather than pluripotent stem cell lines, cell procurement remain under the responsibility of healthcare professionals and hospitals, many of them not-for-profit institutions. The conditions for interactions between pharmaceutical industries that are now investing large sums of money in the development of new manufacturing processes, and academia that is in charge of caring for patients and donors, and thus procures the starting human biological material need to be defined. Existing registries and stem cell banks represent potential assets to tap for accelerated development of these innovative therapeutics. Beyond technical and biological issues, the emergence of these new medicinal products raises specific questions related to the ethical, legal and societal aspects of marketing and selling products manufactured from human material.

70 Christian Chabanon , Professor of Cell Biology, Aix-Marseille Université (AMU) School of Medicine & Head, Cell Therapy Facility & Curator, Tumour Bank / Biological Resource Centre (BRC) in Oncology, Institute Paoli-Calmettes & CRCM, Comprehensive Cancer Centre, Marseilles, France. Secretary: Cell Therapy & Immunobiology Working Party, European society for Blood and Marrow Transplantation (EBMT), Barcelona, Spain.

2. Prof. Dr. James A. Adjaye: "Patient-derived induced pluripotent stem cell lines: applications and ethical concerns" [71]

Prof. Adjaye reported on patient-derived induced pluripotent stem cell lines. Generation of induced pluripotent stem cells (iPSCs) from somatic cells by the over-expression of the embryonic transcription factors, OCT4, SOX2, KLF4, and c-MYC has revolutionized stem cell biology and regenerative medicine. These cells are comparable to human embryonic stem cells in that they can be induced to differentiate into cell types representative of the three germ layers-mesoderm, endoderm and ectoderm. iPS cells are useful for (i) studying gastrulation, (ii) understanding disease mechanisms, (iii) toxicology studies (iv) drug screening and (v) treating patients, all without the ethical controversies that surround the use of human embryonic stem cells.

Within this framework, he presented their ongoing research employing patient somatic cell derived iPSCs to study (i) Late Onset Alzheimer's Disease, (ii) Nijmegen Breakage Syndrome and (iii) Non Alcoholic Fatty Liver Disease. These iPSC cell lines and data emanating from these studies have generated commercial interests, however problems have arisen as approval for commercialization was not sought from the onset from our patients. Recently, several laboratories including mine have turned to urine derived renal epithelial cells (URECs) for cellular reprogramming. The rational for this is the ease at which urine samples can be obtained, however, they are going to face unanticipated ethical concerns.

71 James Adjaye, Institute for Stem Cell Research and Regenerative Medicine, Medical Faculty, Heinrich Heine University Düsseldorf, Germany.

3. Prof. Dr. Peter Schlenke: "The Vision of Artificial Blood Supply" [72]

Prof. Schlenke is director of the clinical department of blood group serology and transfusion medicine and group leader of the research unit „Hematopoietic stem cell differentiation ". He presented his research activities which aim to better understand the molecular mechanisms to instruct multipotent hematopoietic stem cells into lineage-committed progenitors and mature blood cells. His team has international expertise especially on in-vitro generation of already enucleated reticulocytes in three-phase liquid cultures. Experiments are currently underway to scale up the expansion of red blood cells and to improve the final maturation including the enucleation process and the cytoskeletal remodeling into biconcave erythrocytes. The experimental data obtained serves as basis to translate these findings into a concept of biotechnological manufacturing of carefully phenotyped red blood cells under consideration of the requirements of Good Manufacturing Practices (GMP). In parallel,

72 Peter Schlenke, Department of Blood Group, Serology and Transfusion Medicine, Graz, Austria.

they will extend their research efforts to the adjacent fields of myelopoiesis and megakaryopoiesis as well as to hematopoiesis-associated disease models such as sickle cell disease.

These examples illustrate the complexity of the ethical questions stemming from the development of stem cell research.

Recommendations

Within the EUCelLEX project the process allows to structure information pertinent to stem cell research (e.g. of links, regulations, legislations, directions) and also results such as comparisons of legislations concerning a specific activity between different member states. Therefore, the main benefit is that all information and results become clearly represented and easily available to all partners. The engagement of stakeholders to further discussion, refinement of the general master process or addition of possible use cases paired with interactive discussion via the comment function were possible. Public dissemination were also be facilitated. This will allow ethic committee members or scientists fast orientation to identify the needed information on the regulations applicable to various procedures of stem cell research/therapy within Europe. Also politicians can quickly gain deeper understanding leading to a more process oriented, harmonized legislation.

- **A workflow of the process of stem cells to therapeutic products shows the need for harmonising the regulation to cover all the pathways.**
- **Importance of the links between healthcare and research teams throughout the process (the issue of comparability – animal choice, etc. – is critical to demonstrate basic quality/ security or proof of concepts).**
- **Does the classification is useful? An open classification would allow advances while regulating ATMP.**
- **Discrepancy in the regulation between medicinal products (European competence) and tissues & cells (national competence)**
- **Classification could clarify the translational road.**
- **Does the classification create a blocking of downstream inventions?**

- Focus is on allogenic uses
- Safety of the citizens combined with protection of the market and creation of European innovative companies

(innovation precise flexibility => aims to deliver a quality product at a good price)

- Could we think about a different regulation for autologous and for allogenic products?
- Differences between scientific and commercial definition of products!

References

1. Kriks S, Shim JW, Piao J, et al. Dopamine neurons derived from human ES cells efficiently engraft in animal models of Parkinson's disease. Nature. 2011;480(7378):547-551.

2. Shiba Y, Fernandes S, Zhu WZ, et al. Human ES-cell-derived cardiomyocytes electrically couple and suppress arrhythmias in injured hearts. Nature. 2012;489(7415):322-325.

3. Sundberg M, Bogetofte H, Lawson T, et al. Improved cell therapy protocols for Parkinson's disease based on differentiation efficiency and safety of hESC-, hiPSC-, and non-human primate iPSC-derived dopaminergic neurons. Stem Cells. 2013;31(8):1548-1562.

4. Wang S, Bates J, Li X, et al. Human iPSC-derived oligodendrocyte progenitor cells can myelinate and rescue a mouse model of congenital hypomyelination. Cell Stem Cell. 2013;12(2):252-264.

5. Migliaccio G, Pintus C. Role of the EU Framework in Regulation of Stem Cell-Based Products. Adv Biochem Eng Biotechnol. 2013;130:287-299.

6. McBlane JW. Regulatory landscape for cell therapy--EU view. Biologicals. 2015;43(5):433-436.

Cells, ethics and societal innovation

Report and Recommendations

Virginie Tournay
Alessandro Blasimme

5

What is regenerative medicine made of? From product valuation processes to the measurement of public opinion

Virginie Tournay, Adeline Néron

Over the last two decades, stem cell biology has grown into one of the most prominent and rapidly expanding areas of science. In the meantime, as science becomes increasingly more proficient in altering the biological characteristics of cells extracted from human beings, concerns intensify over the possibility of potentially dangerous side effects due to those technical manipulations once the altered cells are re-injected in a patient. Lightening progress in scientific understanding of stem cell biology has created a widespread expectation to harness its therapeutic potential. Interestingly, the clinical promise of stem cells has taken shape in a complex landscape of – often conflicting – representations about their biological properties, their clinical translation, their legal status, their regulation, commercialization and provision to the public. The community of those who are directly involved in the clinical translation of stem cell research into clinical application is made up of a heterogeneous set of actors (scientists, clinicians, science-based companies, patients – passive public/users – companies, lawyers, bioethicists, regulators, social science scholars, etc.). In controversial cases surrounding the clinical use or the provision of stem cells, those actors can become relevant stakeholders.

The public relevance of regenerative medicine – that is deeply intertwined with its scientific component and related uncertainties – is apparent in current debate about the provision of unproven stem cell therapies directly to patients ahead of clinical certification, as well as in discussions concerning the impact of debate about the development of new cellular therapies on public opinion. The aim of this paper is to reconstruct social imagined scenarios by analysing the discussions and controversies they give rise to. Our work focuses on providing a better understanding of representations of social groups active in regenerative medicine and cell therapies, through stakeholders of the European exchequer. The inventory of individuals and organizations includes those involved in the technologies themselves and also imagined scenarios associated with the technologies that are developed, used and regulated (Appadurai 1996, Castoriadis 1975). These imagined scenarios and interpretations of standards and narratives, not only motivate decision-making but also shape relationships between individuals and groups involved in stem cells research, bio-product developments and therapeutic pathways. Cells are caught up in injunctions and intentions of progress and innovation. For instance, regulating stem cells as drugs or as medical devices demonstrates a different logic underpinning the regulatory options. Thus, the community surrounding ATMPs is steered by distinctions between values and contrasts in priorities that need to be clarified.

Based on both quantitative and qualitative methods we have analysed stakeholder attitudes with the aim of mapping how different understandings of "evidence" come to the fore in regenerative medicine – from biological evidence to social certification.

The first part of the paper makes a list of imagined techno-scientific scenarios related to controversial cases regarding storage, basic research and the clinical use of human cells. Different scales of regulation give rise to supranational, national and intra-institutional regulatory variability, thus involving a large variety of decision-makers. Quality and efficacy requirements, when projected onto novel techno-scientific objects and clinical activities both reflect and reinforce the ontological uncertainty of cellular therapies.

The second part focuses on the publics of regenerative medicine and the way in which institutional actors (scientists, regulators, policy makers) publicly represent them. These publics are made up of patients and "public opinion(s)". In public controversies concerning the administration of unproven stem cell therapies, public opinion has had a strong influence on policy response. However, what is presented by mass media as "public opinion" on controversial scientific issues may not correspond to majority views, nor faithfully recapitulate legitimate interests. By the same token, when public opinion becomes polarized, decision-makers may be led to under- or over-estimate the demands of individual patients seeking access to innovative (albeit still unauthorized) therapies. It is therefore desirable, that decision-

makers keep track of the dynamic formation of expressed opinions around cell therapy. For this reason, this section addresses the measurement of public opinion and its development over time regarding this new promising but controversial area of regenerative medicine. Testing the social acceptability of a biotechnology is different from measuring an electoral preference based on a sample of individuals. Traditional opinion surveys are not adapted to observing the opinion building process. The second part of this paper questions what it means to test the social acceptability of a novel technology from the patient's point of view and using public opinion measurement tools.

Analysing both these levels implies taking systems of actors, institutional materiality (legal instruments and technical processes) and symbolic logic into account. We therefore conclude that the current institutional and regulatory landscape calls for the identification of legal instruments that are aligned with both the societal and the biological dimension of cell therapy. We have identified four areas in the development of cell-based therapies in Europe that require critical attention by policy-makers: 1) information, 2) regulation, 3) governance and 4) public opinion monitoring.

European Union Directives set standards for donation, procurement, testing, processing, preservation, storage, traceability and distribution of human tissues and cells[73]. as a consequence, a common regulatory framework for innovative therapies exists in Europe, one that is intended to facilitate the clinical translation of cell therapies into marketable therapies. The supply of these products is part of a global market of living and circulating products. The regulatory regime is under scrutiny together with its narratives on frontiers and identities when questioning the market of health products of human origin (Kent *and al.* 2006; Mahalatchimy *and al.* 2012). The institutional and regulatory landscape of the manufacture of bio-products calls for ascertaining that legal instruments are in consistency with the social and structural settings where they are developing. An in-depth look at how modes of engagement and partnerships shape a Regenerative Medicine community, reveals rationales associated with the bio-materialities of embryonic or adult, autograft or allograft injected cells, regulatory options, biotechnologies markets and health practices. A public consultation exploring the views of "interested parties" on the regulation on advanced therapy medicinal products has been conducted by the European Commission in 2013[74]. We highlighted the distinction this consultation revealed between mostly private and public sectors.

This part of our analysis is based on a range of qualitative interviews. Based on the analysis of the literature and our previous works, we decided to target five groups of stakeholders: (1) scientists & clinicians, (2) regulators, (3) patients organizations & representatives, (4) industries & lobbyist representatives, and (5) mediators, communicators & intermediaries. Pulling together the five categories, stakeholders and distributed across six European nationalities. Interviewees have been members of several foundations, scientific organizations and/or governmental agencies, at one time or another during their career. All of them are or have been involved with advanced therapies, medical innovation, biotechnology or biomedical research. The 12 qualitative interviews were semi-structured, and included a number of questions designed to create open discussion. The first round of interviews was conducted in Summer 2015, whereas a second round took place in Winter 2015-16. The interviews lasted between two and four hours and were about to gather relevant data on some controversial

73 ATMP Regulation (EC) N° 1394/2007; Directive 2004/23/EC (European Tissues and Cells Directive); Directive 2006/17/EC (Technical requirements for the donation, procurement and testing of human tissues and cells) ; Directive 2015/565 (Technical requirements for the coding of human tissues and cells) ; Directive 2015/566 (The equivalent standards of quality and safety of imported tissues and cells).

74 An analysis of this Consultation demonstrated that measurement of the Directives' effects indicated an environment that is not optimised, a need for coordination, not only between member-States but from research to clinical practices, to tally clinical trials with systems of evaluations and reimbursments of the products. See Blasimme & Rial-Sebbag, 2013.

cases selected on the basis of their ethical and societal relevance with respect to the present regulatory framework. The entirety of the exchanges was transcribed and the full texts were analysed as individual testimonies. The aim of the analysis was to to draw general patterns between and from stakeholders about these controversial cases regarding storage, basic research and clinical use of human cells. To that end, interviews notably ended by submitting an identical selection of key words thematically circling our points of interest, supporting the possibility of relating the interviews to each other thus allowing us to observe general patterns within the group. We were interested in the content and thematic architecture of the discussions rather than respondents' socio-cultural characteristic, and respected the consent forms directing our interviews and agreements made with the interviewees regarding the confidentiality and anonymity of our exchanges. This procedure is in keeping with the approach involved in understanding a community by means of individual answers.

The analysis revealed effects of values, such as quality or efficacy, projected onto techno-scientific objects and activities. Quality and efficacy requirements, when projected onto novel techno-scientific objects and clinical activities, both reflect and reinforce the ontological uncertainty of cellular therapies. Nevertheless, fragmentations and sub-communities of definitions manage to ensure that re-negotiation is systemic, and fundamental to the operational collective dedicated to innovative medicinal products. These results articulate as follows.

1. Heterogeneity

Beyond rules on marketing authorizations and institutional supervisions of products, the first theme aligning itself with this inquiry is the heterogeneous set of valuation processes. It is generally accepted that European Union Directives are not simply executed but adapted in variable combinations corresponding to institutions and objects. However, a more in-depth investigation reveals an even broader variability of interpretations. Relationships to standards and norms encounter several narratives as shown by a few quotes from distinct stakeholders:

> *"We separate regulatory approval depending on whether it's cost effective.*
> *For now I think it's better to focus on quality, rather than how much a product costs.*

The problem in this community is that they're solely focused on that part."
"Regulation of ATMPs is based on the assumption that if you want to use them you have to make sure that they are safe. To sell, you must prove safety and efficacy."
"Flexibility is about how you demonstrate, how you get the data on quality and efficacy"

There are no direct common denominators for interpretations regarding the safety, the efficacy or the quality of a product in court, for marketing authorization committees, trade or people's blood and bodies. Descriptive and normative contents of these extended qualitative interviews showed conflicting representations among key stakeholders involved in this community. Among these, the trust granted to medical research nourishes confrontations in clarifying definitions of distinct types of evidence (evidence of health protection, of investment returns, of procedures adequacy, etc.) and of risk (of unproven treatments, related to ethics, to health systems, to relations to medical knowledge and expertise, etc.). Apart from definitions of notions, institutions were also subjected to different views. Our data followed how the same individuals or institutions were described as "central" or as "marginal", how the same technological objects were qualified as "good" or as "dangerous", the same dynamics between stakeholders were "efficient" or "complex" according to respondents. The followings quotes, also from different stakeholders, reflect this range of views:

"Helping the patient is the basis of all our activities and thoughts"
"The whole field is being used as a way to shift from one view of health by governments and doctors, to a vision of health no longer related to Medicine but only to markets, where the doctor is replaced by a provider, a seller"
"People worry too much about the regulators, when they should worry about real possibilities of return on investments"
"When doctors believe that they don't need the patients anymore, they lose them. ATMPs show what Medicine should be"

Comparing the different views shows how heterogeneity also characterizes definitions of individuals and organisations, in terms of their objectives and activities. Uses of human body elements imply manipulation of the living, relations with the cell donor, ownership, commercialisation or collective choices and individual rights. All of the above provide answers to arguments about value. Scientific reasoning, laboratory and clinical proof and the mission of academic research to generate evidence are contrasted by political, social and financial strategies among the categories of stakeholders we identified and followed along this non-linear path from science to technology and innovation. Defences and oppositions regarding the characteristics and impact of the social acceptability of the current, structural state of cell therapies make notions of probity and validity rather vague, and linked to quasi individual definitions. The foundations of the flourishing cell therapies industry are formed by patients suffering from life-threatening illnesses, regulatory agencies promoting the importance and increase of regulatory frameworks, scientists promoting fundamental research and companies defending their products. Positions are firm and distanced from shared interests. These definitions and priorities regarding experimentation, property or solidarity occurred in several places: hospital rooms, private laboratories, parliamentary commissions, lobbyist offices, judges' chambers, scientific journals, public media, etc. This spatial anchoring supports the illustration of how imagined scenarios are maintained, naturalized and localised in specific cultural framings. Denominations test the strength of the standards promoted by public administrations, as scientific, legal, political worlds do not share operational fundamental principles. Therefore, the variety of definitions and of approaches that was explicitly testified to, dismantles the united community narrative formulated in the arena of stem cell research and applications.

> *"You don't have the scientific proof this therapy is helpful or not, but the person is going to die soon. As long as you don't have proof it's helpful, you don't know if you're helpful, but neither that you are not. Give science a chance to try and people a right to try"*

2. Moving Targets

Connecting the interviews leads to patterns of combinations between clinical values, commercial

values and human rights values. Accountability, for its part, does not garner unanimous support, either in an inherent definition or regarding its addressees. The “Free” and “Common” Market is subject to both opposition and compliance, as a process and as a purpose, which confirms its intertwining in the process of cell therapies, diverted from the sole interest of public health. The broadness of the answers shows an overview of the stakes and the perceptible core of uncertainty. For instance, the history of biomedical innovation trajectories reveals a distance between proof of efficacy, utility, and provision. The change of scale from trials to recognized therapies for stem cells are part of a long-term inheritance of medical innovation developments, from heart and kidney transplants to genetic diagnosis. Here, the definitions of science lead to a dilution of expertise, when patients who purchase access to a product by themselves seclude the very principle of testing and scientific validation. In addition, our observation shows the impact of the gravity surrounding the medical conditions involved.. Biology is accused of being behind on therapies, authorities of being too slow to grant access, while buying access goes from being a solution to being merely a “comfort”. Overly late access makes it impossible to gather strong clinical data, in cases where the effects of a potential treatment cannot be evaluated if the patient’s condition is too advanced. Regenerative medicine illustrates the tension surrounding the experimentation phases of a therapeutic product and contradictions between scientific and social normalizations of its trial phase outcomes. The current European regulatory framework for stem cell uses, aiming to translate scientific knowledge into therapeutic products, has reached its limits in what it manages to provide which serve as a basis for patients to claim early access to these therapies

> *“A lot of the therapies we’re talking about are novel, there are elements of uncertainty. So you need a critical friend to talk to about what you’re doing”*

3. Community

The interviewees themselves supported the idea of structuring a “community” [75]. Such a community must, consequently, be analysed. A vocabulary of constraint and obligation surfaced - “important”, “mandatory”, “necessary” and “unavoidable” were recurrent qualifying adjectives used in the interviews. This emphasises the need to draw boundaries for the development of cell therapies.

75 By community, we mean that representations of stem cell practices inscribe an imagined future into cellular materiality, thereby constituting socio-technical imagined realities. This material architecture affects the general organization of the network. Individuals involved in stem cell issues actually share a common language, technical devices and networks?

These first distinctions see ATMP regulation[76] as an instrument of social dynamics between producers and doctors, and enshrine cell therapies at the crossroad between marketing enterprises and public health hospitals. The difference described between "hospital exemptions"[77] and "cell tourism"[78] was that one is sanctioned and the other is not. But both illustrate value negotiation in individual access to the promise of cell therapy. As experts, scientists and regulators draw lines of norms and definitions, these lines represent the frontiers of the community and ramparts to perpetuate its own existence. And this is despite the lack of a strong alliance in granting value to bio-materialities. The perspective of practical opportunities to "translate" the results obtained from the meta-analysis of an ATMP community into a pooling of interests leads to: sellers for customers, patients for therapies, care professionals for solutions, clinical trials for participants, scientists for experiments, innovation for funds, regulators for issues, lawyers for arguments. The focus on how to connect demand and response exerts a pressure on the community's foundations - patients and their health. The shared imagined scenario is based on promises: the promise of new applications for science, of new therapies for diseases, of returns on investments and of regulatory adaptations. In short, promise is the driving force.

The various entities maintain themselves respectively by projecting an ideal community. The mutual dependence of the sub-communities (such as material suppliers, stem cell networks, regulators of therapy medicinal products, participants to clinical trials or medical tourism etc.) does not mean mutual comprehension or assistance. The dynamic has more resemblance to an ecosystem in which each entity benefits from the others than a fully established, stable cooperative system. Because "everyone wants to make this work" by co-developing, the parties interact from research to clinical use. This progression allows some of the rationales contained in applications of European Directives to be reconstructed. Regulations impact identities and social dynamics, and the coherence of an imagined community clearly derives from techno-scientific practices (Anderson, 1983, 2006). The result relates to modes of engagement and identities by creating a common world. This does not happen because logics are internalized, or because different narratives are gathered together as part of a common interpretative blueprint, but rather because the connections between stakeholders allows them to discuss their conflicting representations and discourses. In the current landscape, the introduction and

76 Regulation (EC) No 1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products

77 Possibility to use innovative therapies without a marketing authorisation, article 28 (2) of the Advanced Therapy Medicinal Products (ATMP) Regulation

78 Access to usually unproven therapies in another country than the one of residency of the patient

negotiation of definitions and values granted to cells act as a stabilising element. Our interpretation is based on a community built around questioning rather than sharing definitions. The frontiers drawn by the regulatory position are not between members of the collectives working on cell therapies but rather around them. The collective is characterized by permanent mutual redefinitions of the value of a cell injection and evidence of its significance - whether this significance is financial, scientific, therapeutic, or related to public or individual health care. Therefore, regulating stem cell usages does not call for limiting uncertainty but rather for identifying and supporting the potential for negotiation. Current legal, scientific and social categorizations entail a focus on mutual influences between institutions and technologies, laws and specific innovations.

In this project where we look at how identities are created around technologies, one striking result has been to witness a major defence of the existence of a community and the lack of unity therein. Entertaining the promise of stem cell therapies calls for communication among this community and its sub-communities of representation and definition. A densification of institutional structures and regulatory layers or an extension of process-oriented regulations would not harmonize logics and rationalities. Even as a whole, current supranational regulation is considered to be “harmonious” while widely accepted as necessarily being a step behind patients, research and corporate needs. There is no sign of deep distrust or dissatisfaction regarding regulation. Neither its flexibility nor its adaptability is in question. Suggested outputs of “technical harmonization” or “regulatory convergence” to soften the variety of categories under which cell products are included might not particularly strengthen the ATMP community. Not only might convergence of categories and regulation more generally risk diluting the current structuration in place, it might also lead to more imbalance, notably between European member-states. Non-harmonizing countries may simply be unwilling or unable to draw up a scientific and financial plan. Indeed, the classic competitiveness in innovation, and in scientific and economic developments, is relatively neglected in the narratives we collected. One core issue is about how cell technologies are included in national economic systems. One preoccupying factor is the cost of reimbursements to innovators, developers and distributors, directly or indirectly through social security systems. Rather then, stronger partnerships between scientists and regulators, between scientists and patients, between developers and consumers in advanced medicinal products are reliant

on better mutual understandings. These mutual understandings would allow the thus strengthened community to embrace the flexibility in regulations as a collective. Such dialogue interfaces are badly needed. Interconnections, ties and bonds within the community would result from times and places set aside for those involved in cellular therapy issues to express themselves and understand the respective rationalities at play.

Do regenerative medicine publics exist?

The regenerative medicine market presupposes the setting-up of various publics, more or less directly concerned with its promises and expectations. All discourse, all web content dealing with regenerative medicine provide a specific representation of stem cells that implies a target public. These publics can be existing, virtual or imagined and the target public can be stem cell producers and operators (both academic and industrial), patients, regulators, decision makers or “public opinion”. We identify those stakeholders whose practices do not rely on specific expertise of stem cells and categorise them as “external” publics. From “non-expert patients” who are included in the stakeholders, to “public opinion” referring to people who have heard about these new biotechnologies, these categories do not express themselves but their opinions are represented by other groups or, evaluated through tools for measuring opinions. The question arises as to what extent it is possible to talk about specific audiences of this emerging market since its characteristics are not directly accessible by regulators and policy makers. Patients’ representations and imagined scenarios about the promises raised by the use of Stem cells potential or proven to exist, are only indirectly reported which confirms the distinction between institutionalized-driven imagined scenarios and marginalized ones. Although, conceding to biological uncertainties, the technical complexity of cell therapies is also accompanied by social uncertainties. This reiterates our invitation to clearly distinguish between real shared imagined scenarios and those emerging from certain dominant and influential groups.

Is public opinion consistent? In national and European contexts where the socio-economic impact and social acceptability of emerging technology become indicators as important for public decision-makers

as the scientific assessment of risks associated with their development, it is important to have reliable indicators and to provide limits to what is being measured to policy makers. The political issue is all the stronger since the production of trust indicators regarding biotechnologies modifies the institutional culture of the regulation of innovations. What does it mean to test the social acceptability of a novel technology? To what extent is it possible to determine the social acceptability of a technology that has not yet been appropriated by the population in general?

1. Patients

Our work on the network analysis data has shown, that "patients" are not involved in accountability nor are mentioned in the translational process, nor have networking abilities. They are, on the other hand, at risk and need to be protected by quality products and regulatory tools. Because they are excluded from the above, their position is only indirectly reported. The analysis is not that because patients were not the major stakeholders encountered, an imbalance was produced. The result is a major account of projected intentions and justifications relative to patients, as individuals or as groups. Hence, the dominant narrative[79], transmitted by dominant operators, is indeed the need to carry on the strategy of projection on patients rather than including them in a more participative way. Yet, such a co-dependant system leaves no possibility for therapeutic freedom. One example - scripted multiple times – relates to cell tourism experiences that led to deceased patients. Freedom to purchase hope is then pointed out to be deleterious to the ATMP field. Freedom of access is replaced by "early access" and "expedited programs"[80] which must be more centrally controlled. Mostly run by medical doctors, from Intergovernmental Organisations to regulatory European Commission boards, the medical community tries to remove the path where patients interact directly with business, in a provider-consumer relationship that would neglect medical advice and intervention. This delegation of patient's voices led us to consider the struggle against the uncertainty that including a new group would signify. Patients, NGOs and medical charities, mentioned as players in the arena, are far from the reality of individual patient. Blamed or highlighted under a lexicon of "society", direct patients are a danger to the ATMP community as it is "society" that refuses risks and insists on high standards. Even if associated with an insistent demand for solutions to current problems and healthcare challenges from governments, patients are held responsible for pushing for so much elimination of risk that this

79 Only a few web entities are frequently cited or have a strong bridging position. This network is highly segmented and this chart in particular shows a clear separation between established international scientific networks (dominant narratives) and private companies (very numerous but seldom cited)

80 These new modes of regulation for ATMP aimed at putting the products on the market at an early stage of their development and at gathering data on safety from the real life utilisation

has been at the expense of productivity. Moreover, patients seek cures, whatever these might be (medication, injections, surgery, etc.), with no understanding of the complexity and technical difficulties inherent to these therapeutic options. The presence of patients in narratives of the ATMP community distorts the charts. But it stops there [81].

2. The measurement of public opinion

In traditional studies, sample-based public opinion surveys are based on a number of objectifying assumptions. Usually, the notion of "public opinion" refers to a target group made up of a voting community (whether they vote or not) with the idea that the general opinion is based on the counting of individual opinions. Thus, "public opinion" is defined by two dimensions: firstly, the number of individuals and secondly, the content of opinions. Topics such as scientific and technological choices are unusual in political marketing surveys because they are related to complex expertise. Unlike surveys on partisan preference issues, the topics are not systematically associated to political concerns for citizens. Moreover, a significant portion of respondents are ignorant of or politically indifferent to the topic of biotechnology. Regarding these themes, the sampling is a very important issue, more especially the specification of the sub-population used to define the representative sample of the surveys. For instance GMOs, bio-carburation or stem cells are not necessarily related to a specific *a priori* community. Indeed, it is very difficult to interpret the answers of respondents who have no ties, or involvement (or "concern" for Callon, Lascoumes and Barthe, 2001) with the subject on which they are questioned. Traditional surveys do not provide information about the propagative strength of acceptability of biotechnologies, or a clear idea of the consistency of public opinion itself. The responses obtained in classical opinion polls are representative of a generally non-specialist population or to intervene directly in public debate. In addition, the responses to questioning provided by individuals who have no specific ideas about a theme as complicated as regenerative medicine, are based on considerable bias. The opinions given by the respondents are strongly dependent on the survey system, that is to say the way in which the questions are formulated. Here are some examples from the 2010 Eurobarometer.

81 As patients are quite absent from institutions as deciding agents, we found ourselves reproducing the indirect report of patient representations. The patient organizations we contacted either did not answer or redirected us towards "more competent colleagues", who happened to be medical doctors and regulation specialists. Even if indirect representations were included in our research, we outline this social group as being isolated in these patterns of regulation.

Formulation of questions about stem cell research implicitly suggests a kind of transgression from an old research order. To answer them most accurately, people should have a precise understanding of existing legal frameworks and medical habits regarding the elements of the human body.

> *« Stem cell research involves taking cells from human embryos that are less than 2 weeks old. They will never be transplanted into a woman's body but are used to grow new cells, which then can be used to treat diseases in any part of the body. Would you say that...? »*

Although a majority of European citizens approve of embryonic stem cell research, 51% only approve of it as long as strict laws are in place. Results are interesting in country by country analysis, showing that approval is more widespread in Denmark, the United Kingdom and Iceland, while disapproval is most widespread in Austria. Looking at the sociodemographic data, religion and education influence approval rates. Furthermore, Europeans are more supportive of adult stem cell research than of research involving embryos. If the observed variations in approval are related to socio-professional categories and to the nationality of respondents, analyst interpretations cannot ignore the question of knowledge of these highly technical subjects.

Another example: descriptions of biotechnologies are often associated with a transgression of the natural order, causing some form of ethical mistrust. Synthesis biology, which is a continuation of existing practices, appears in the questioning as a discipline that breaks with past approaches.

> *"Synthetic biology is a new field of research bringing together genetics, chemistry and engineering. The aim of synthetic biology is to construct completely new organisms to make new life forms that are not found in nature. Synthetic biology differs from genetic engineering in that it involves a much more fundamental redesign of an organism so that it can carry out completely new functions"*

There is an implicit opposition between what is natural and what is not. The effect is all the more subliminal as people are not specialists in synthetic biology. The difficulty in interviewing non-experts on these issues is almost unsurpassable. The survey does not provide information on the social representations associated with these biotechnologies, but rather shows the effect of the questions on respondents. This does not prevent the analysis of opinions according to several variables such as socio-professional categories and nationality. But the general responses are highly dependent on how the questions are formulated given the general misunderstanding of the public regarding these problems. One hypothesis is that the reliability of public opinion indicators for scientific and technological choices is more dependent on the identification of opinion-makers rather than on the «reasoned» questioning of a sample of individuals. We have proposed a new methodological tool in addition to the surveys in order to reinforce the reliability of the general public's knowledge of the subject. In particular, we show that digital tools could be complementary allies to realising traditional opinion pools. Our structural study based on a web-big-data-gathering provides serious indications regarding opinion-makers and shows the discrepancy between the attitudes of Europeans towards the development of regenerative medicine and concrete practices. Europeans considering this technological development must be very framed while remaining very accessible. Previous analysis of web networks performed in the course of this project (not published) shows rather the predominance of local regulatory contexts and the development of unregulated medical tourism based on unproven but promising therapies. The conjugation of the two measurement methods of opinion (digital and conventional methods) clearly shows the distinction between what belongs to **social acceptability** and the nature of **technological appropriation**.

3. Dealing with trading zones: the role of public decision-makers.

The granularity of the "imagined communities" is extremely complicated. The quest for sampling representativeness obscures misunderstandings by the public, and their consequences. Technical uncertainties, diversity of regenerative medicine practices and the interpretative limitations of opinion indicators have led us to identify four main dimensions corresponding to existing "trading zones" (Galison 1997) in the huge diversity of stakeholders dealing with translational aspects of stem cell research.

Recommendations

Policy aims for the governance of regenerative medicine must take points into account (1) information, 2) regulation, 3) governance and 4) public opinion monitoring). We propose recommendations for each of these four dimensions.

1.
Cellular therapy has required the crafting of specific classification criteria to assimilate advanced medical products to medicinal drugs, and to regulate how these products reach patients both in research and in clinical contexts. However, residual ambiguities in this classificatory system remain and should be addressed in order to deal with dubious attempts at bypassing the central marketing authorization procedure. EU policymakers should encourage further mediation between science and citizen (public understanding of research) by the development of exhibitions highlighting the complexity of working with living matter and attempting to turn it into therapeutic material.

2.
Policy should be better equipped to enforce regulation of therapeutic claims that, during phases of public hype and expectation of novel clinical breakthroughs, might lead patients to accept unreasonable risks or to be exposed to fraudulent therapies. The legal categorization of cell products must be in accordance with their biological properties. This requires guidance on the part of the EMA to refine the technical criteria that determine how a given product should be considered. Legislators should not try to adapt existing classificatory schemes in the course of a public controversy with the aim of accommodating the demands of any of the contending parties.

3.
Cell-based therapies represent a rapidly evolving field of scientific research, medical progress and societal change. EU policy-makers should find institutional ways to come to grips with such an elusive scenario. In particular, policy-makers should be able to monitor how expectations and initiatives evolve around cellular therapy in order to anticipate future challenges before the breakout of hard-to-manage public controversies. This is related to institutional design issues. In particular, regulatory agencies should facilitate upstream communication between sponsor and research institutions on one side and patient associations on the other, in order to foster

accountability among relevant stakeholders. Improving the "institutional readiness" of institutions developed by the ReGenableMed consortium, this concept describes the capacity and willingness of key pre-existing organisations to adopt, respond to and use advanced therapy medicinal products as part of regenerative medicine. This refers to the plasticity and adaptability of institutions. Based on this idea, we argue for the need to develop upstream accountability among stakeholders.

4.
In public controversies concerning the administration of unproven stem cell therapies, public opinion has had a strong influence on policy response. It is therefore desirable, that decision-makers keep track of the dynamic formation of expressed opinions of cell therapy. Testing the social acceptability of a biotechnology is different from measuring an electoral preference based on a sample of individuals. Traditional opinion surveys are not adapted to observing the opinion building process. A digital mapping of expressed opinions should instead be adopted as a means to monitor (as opposed to polling) levels of social acceptability. Social acceptability and technological appropriation do not have the same meaning. Regulatory agencies should encourage digital analysis of the controversies emerging around novel technologies, i.e. exploring the relations between actors (exploratory network analysis). To this aim, academic researchers with specific training in exploratory network analysis could be charged with the task of monitoring how public opinion evolves over time concerning new promising but controversial area of biotechnology – such as regenerative medicine.

Detailing the forms of engagement, the bureaucracy within collective and individual interests, private and public viewpoints, brings the "hope market" face-to-face with the concrete investments and applications of cellular therapies. The hope is that such therapies will succeed in preserving youth, improving health and preventing death. Currently, cell therapies are focussed on an ageing population, in a bio-politics of care and responsibility, rather than on rare and serious diseases.

References

Anderson Benedict. Imagined Communities. Reflections on the Origin and Spread of Nationalism, London, Verso. 1983. Revised edition, 2006.

Appadurai Arjun. Modernity at Large. Cultural Dimensions of Globalization. University of Minnesota Press, 1996.

Bianco Paolo, Xu Cao, Paul S. Frenette, Jeremy J. Mao, Pamela G. Robey, Paul J. Simmons, Cun-Yu Wang. « The Meaning, the Sense and the Significance: Translating the Science of Mesenchymal Stem Cells into Medicine ». Nature Medicine. 2013.

Bianco, Paolo. « Don't market stem-cell products ahead of proof». Nature, 2013

Bianco Paolo, Roger Barker, Brüstle Oliver, Cattaneo Elena, Clevers Hans, Daley George Q., De Luca Michele, et al. « Regulation of Stem Cell Therapies under Attack in Europe: For Whom the Bell Tolls ». The EMBO Journal, 2013.

Bowker Geoffrey C., Star Susan L.. Sorting Things Out: Classification and is Consequences, Cambridge, MIT Press (2000).

Baert Patrick, Rubio Dominguez (eds.). The Politics of Knowledge. Routledge. 2011.

Blasimme, Alessandro, 2013. Translating stem cells to the clinic: scientific societies and the making of regenerative medicine. Quaderni 29–44.

Blasimme Alessandro, Rial-Sebbag Emmanuelle. «Regulation of Cell-Based Therapies in Europe: Current Challenges and Emerging Issues». Stem Cells and Development. 2013. Castoriadis 1975

Dusko Ilic, Stem Cell Banking. Springer. 2014.

Farrell Anne-Maree. The Politics of Risk and EU Governance of Human Material. Maastricht Journal of European and Comparative Law, Vol. 16, n°1, p. 41-64, 2009.

Faulkner Alex, Kent Julie, Geesink Ingrid, FitzPatrick David. « Purity and the dangers of regenerative medicine: regulatory innovation of human tissue-engineered technology. School of Social Sciences. 2006.

Culme-Seymour Emily and al., « A decade of cell therapy clinical trials (2000–2010) », in Regenerative Medicine, vol. 7, n°4, p. 455-462, July 2012.

Gonçlaves Maria Eduarda. « Risk and governance of innovation in Europe: an introduction ». Technological Forecasting and Social Change. 73, n°1, 2006, p.1-12.

Hyun, I., 2013. Bioethics and the Future of Stem Cell Research. Cambridge University Press.

Hug, K., Hermerén, G., 2010. Translational Stem Cell Research: Issues Beyond the Debate on the Moral Status of the Human Embryo. Humana Press.

Jasanoff, S., Kim, S.-H. (Eds.), Dreamscapes of Modernity: Sociotechnical Imaginaries and the Fabrication of Power. University of Chicago Press, 2015.

Jasanoff, S., Kim, S.H., "Containing the atom: sociotechnical imaginaries and nuclear power in the United States and South Korea", in Minerva n°47, p. 119–146, 2009.

Kent, Julie. Regenerating bodies: tissue and cell therapies in the twenty-first century. Routledge, 2012.

Kent Julie, Faulkner Alex, Geesink Ingrid, FitzPatrick David. « Towards governance of human tissue engineered technologies in Europe: Framing the case for a new regulatory regime ». Technological Forecasting and Social Change. vol. 73 n°1, p. 41-60, 2006.

Mahalatchimy Aurelie, Rial-Sebbag Emmanuelle, Tournay Virginie, Faulkner Alex. « The legal landscape for advanced therapies: material and institutional implementation of

European Union Rules in France and the United Kingdom». Journal of Law and Society. 39 n°1 2012 p. 131-149.

Stephens Neil, Paul Atkinson, Peter Glasner. Institutional Imaginaries of Publics in Stem Cell Banking: The Cases of the UK and Spain. Science as Culture, 2013.

Webster Andrew, Haddad Christian, Waldby Catherine. «Experimental heterogeneity and standardisation: Stem cell products and the clinical trial process». BioSocieties 6 (2011): 401–19.

Umbilical Cord Blood Banking, Research and Clinical Applications: Overall Recommendations

THERE IS A NEED IN EUROPE FOR:

- **Clear policies for the governance of biobanks and UCB (umbilical cord blood) banks in order to ensure transparent and equitable access for both research and therapeutic use.**
- **More detailed guidance from professional societies on the respective responsibilities of data/sample custodians so as to ensure respect of donor consents.**
- **Interoperable core elements of consent to biobanking and UCB for research and therapies.**
- **Clarification on the complementary oversight roles of research ethics and data access committees.**
- **Publicly accessible websites, newsletters and social media sites on biobanking and UCB so as to engage and address the interests and perspectives of participants.**
- **Increasing scrutiny and monitoring of the role of commercial entities in biobanking and UCB banks.**