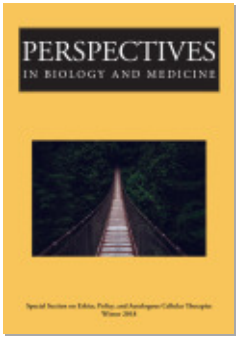
Between the Local and the Global: *Evaluating European regulation of stem cell regenerative medicine*



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evaluating European regulation of stem cell regenerative medicine

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ABSTRACT Current European regulations hinder the compilation of the evidence that would be required to bring safe and effective autologous stem cell–based interventions (SCBIs) into standard clinical care. European agencies have expanded their regulations to cover all new SCBIs and research. They establish demanding conditions for cell retrieval, processing, and application. Drawing on empirical sociological findings from the implementation of the first phase III stem cell clinical trial in Europe, this article examines ethical problems effected by that policy, such as that the costs of bringing treatments to market means new autologous SCBIs may remain untested and that this plays in favor of the growing direct-to-consumer market, and that the research

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pathways in regenerative medicine and the role of clinician-scientists in developing new treatments are restricted, because the regulations are biased to enable specific SCBIs that are of interest to industry. This situation contradicts the moral and social concerns in favor of new treatments and patient interests, which the regulations supposedly safeguard. To align the aims and effects of policy better, European regulatory authorities should reconfigure their regulations to advance a fair and effective governance regime that allows pursuit of all promising SCBIs.

The history and context of the public policy regarding stem cell research in the European Union are complex. The regulations respond to and aim to realize political and economic goals across a large region that is culturally diverse, as well as addressing moral judgments on a contested emerging area of research. This history and context are relevant for the arguments developed here in relation to autologous stem cell research and how it is affected by those regulations.

The EU is currently an open market across 28 countries with different languages as well as varied cultural, religious, and political histories. Bridging the diverse traditions and their corresponding local policies and regulations is often a challenge. Regarding stem cell research, these differences have been well analyzed; the respective policies in individual countries range between controlled permissiveness and the prohibition of research on human embryos (Bender, Hauskeller, and Manzei 2006; Hauskeller 2004). A widely shared sense of respect for early phases of human life finds expression in the affirmation of embryo-derived and genetically altered cell lines for biomedicine in the United Kingdom and Sweden (which is administratively closely monitored), and in the outlawing of the destruction or genetic alteration of human embryos in countries including Germany, Italy, and Poland. (For the most recent update on country policies see EurostemCell 2017.) Researchers and institutions have defended the position that somatic—or "adult"—and autologous stem cell research, as well as therapies based on them, are less morally and ethically problematic than work with human embryonic stem cells, and therefore research with adult cells and autologous applications should proceed (Punzel 2002). The tensions between national attitudes and regulations concerning research using human embryos have affected many EU policy areas, including decisions about EU investments in human embryonic stem cell (hESC) research (Joliff-Botrel and Perrin 2008; Salter 2007). In its *Recommendations on the Ethical Review of hESC FP7 Research Projects*, the European Group on Ethics (EGE) states that,

> EU projects can be funded only if no suitable alternatives to human embryonic stem cells can be found and the absolute necessity of using hESCs has been scientifically justified and evaluated. With regard to possible alternatives to hESCs, the first factor to consider is the possible use of adult human stem cells. . . . [There are] diseases that may be cured in the near future by using adult stem cells . . . , for which the clinical potential of adult stem cells looks very promising. (EGE 2007, 27)

The EU is also designed to pursue political and economic motivations and political aims, however. Its driving values and policies are not easily squared with this balancing act of streamlining policy in a diverse moral landscape. The EU primarily aims at economic and social integration and advancement for a market of ca. 500 million people. Its institutions develop and agree to strategies of investment into research and education, among other areas, and to policies designed to achieve common progress and shared standards. For the timeframe of translating stem cell research into clinical applications, of relevance are two 10-year development plans aimed at growing the EU into the most competitive and dynamic knowledge-based economy in the world—namely the "Lisbon Strategy," agreed upon by the European Council in Lisbon in 2000, relaunched in 2005, and subsequently confirmed in 2010 as the strategy "Europe 2020."

The goals of the Lisbon Strategy included raising investment in research and development to 3% of GDP. A new method was developed to achieve the goals set out, the so-called "Open Method of Coordination" (COM), replacing or better complementing the approach previously adopted to achieve economic integration, namely the setting of legally binding commitments. COM consists of developing guidelines, benchmarks, and platforms for sharing best practices, in order to enable degrees of coordination not only in targets but also in practice, and to facilitate cooperation and synergies of scale between countries. The aim is not to formally harmonize, but to stimulate initiatives and diffuse information. This method is still pursued in Europe 2020, which aims at the creation of a "smart, sustainable and inclusive economy" (ECR 2010).

In the wake of the intense debates about the ethics of hESC research at the start of the 2000s on the one hand, and the Lisbon Strategy on the other, a set of tight regulations has been established. The regulations aim to further research with human cells and tissues in a safe and traceable manner, and to unify practice in biomedical research and clinical trial conduct, without having to solve the substantial moral disagreements around this research. The regulations are largely technical: they respect the fact that some stem cell research–related practices are not allowed in certain countries, and they stipulate that for those who engage in this research, the *modus operandi* is clearly defined. The morally contrary positions are untouched—every country can, as in the established principle of subsidiarity commonly used in EU regulations, introduce rules stricter than those prescribed by the commission (Raffaelli 2018).

This subsidiarity principle that leaves, as far as possible, detailed legal regulations to individual partner countries has led to forms of division of labor and international exchange. Research projects using hESCs operate across countries that do and do not allow this type of research, by using division of labor and exchange of samples and data across Europe (Liverani 2011). Similarly diversified cross-border private markets have emerged for cell-based services and clinical treatments (Beltrame 2014, 2018; Tanner et al. 2018). This allows scientists and

consumers across Europe wider opportunities than they would enjoy in any single one of these countries. Concerning the research investment strategy, direct investment into hESC research has been balanced with investment into somatic and autologous stem cell research. The specific autologous stem cell trial on which I report below would not have been possible without this balanced funding strategy.

The EU is a potentially large market for regenerative medicine. For biomedicine that relies on clinical trials to bring treatments into the clinic, an economy of scale is arguably important, as is a centrally managed unified set of standards. The latter builds a platform for advancing research and new therapies, and it is a starting point for a competitive advantage of the EU's science and economy. Hence, the EU has put into place compulsory directives and regulations of a lesser legal status with which all research with human cells and tissues must comply. The implementation of these directives and regulations is overseen by the European Medicines Agency (EMA), which cooperates with national or professional societies, such as the International Society for Stem Cell Research (ISSCR). The latter has issued the "Guidelines for Stem Cell Research and Clinical Translation" (2016), which have been widely promoted (Daley et al. 2016; Kimmelman et al. 2016).

Not only do moral and political traditions differ across the EU, so too do health-care systems and reimbursement practices. Competitiveness in this future marketplace may benefit from an integrated world-class scientific research community and a large patient base to conduct phase III clinical trials. Within this environment of tight controls on very specific practices, and without overarching or unifying policies aimed at integrating cultural, moral, or institutional practice in others, Europe has seen a diverse and unregulated market develop, ranging from private umbilical cord blood banking to clinics that offer unproven SCBIs that are not validated as efficacious.

In the face of a consumer market for such treatments that has developed across many countries worldwide, European regulators aim to prevent such SCBIs from being offered (Turner and Knoepfler 2016). The circumstances that fostered this market are complex (Petersen et al. 2017), but the promises and hype over the potential cures from stem cells certainly helped build a climate of risk-acceptance among the public and patient groups (Petersen and Seear 2011; Ryan et al. 2010). The agents acting in this direct-to-consumer market for autologous and other cell therapies have been heavily criticized by professionals in science, medicine, and ethics who argue that these treatments are expensive, not validated, and have led to individual patient deaths (Lysaght et al. 2017). Yet despite these criticisms and regulations that attempt to prevent it, a diverse market for unproven treatments, mostly with autologous cells, has developed.

It has been argued that clinicians offering such treatments flaunt professional standards (Petersen, Seear, and Munsie 2013), and although most of the literature

analyzes markets other than those in Europe, individual cases such as the death of a child at the German "X-Cell Centre" have been discussed (Mendick and Palmer 2010; Tanner et al. 2018; Tuffs 2010). Many bioethicists have called for international coordinated action to "reduce the risks of direct-to-consumer marketing of unproven stem cell treatments" (Sipp et al. 2017). Against them, patient activists have demanded that their moral rights to access potentially life-saving treatments must be responded to on grounds of compassion (Adriance 2014; Petersen et al. 2017). This situation could be resolved by trials that prove whether or not an autologous SCBI is efficacious. Yet, if the regulations in place prevent the conduct of such trials, patients' hopes and expectations remain neither fulfilled nor disappointed, and the emerging private consumer markets flourish on the basis of ambiguity and lack of reliable data.

Regardless, this general situation seems to indicate that stringent regulation of stem cell research is only partially effective. It channels and streamlines research pathways across Europe, but it cannot prevent the use of stem cells in clinical applications with doubtful efficacy. The marketing of stem cell applications, especially with autologous cells, is difficult to control, whilst simultaneously researchers who want to conduct scientific trials to establish the efficacy of these applications must navigate a fractured patchwork of European directives and conditions that make such trials nigh impossible (Hauskeller and Baur 2017). Because local regulations and cultural practices of medicine differ, medical teams in Europe offer different forms of SCBIs. Patients and medical staff in a country such as Germany, which has put great effort into strictly controlling research using hESCs and genetically altered cells, seem prone to opting for unregulated uses of autologous or non-embryonic cell types in clinical application. The publicity surrounding the potential clinical promise of adult and autologous cell treatments seems to have caught on, although the efficacy of many such treatments is not validated, and neither are their side-effects or the risks to consumers. Examples for this are the case of the X-Cell Centre or the many offers of untested so-called fresh cell cures for rejuvenation and for many disease conditions, advertised globally online (Frischzellenkur 2017; Petersen et al. 2017; Tanner 2018).

European harmonized regulations may have a number of unforeseen effects on autologous SCBIs. One effect is that potential treatments with autologous stem cells may be made so expensive that they become unaffordable. The initial advantage, that autologous treatments can be locally and readily applied, is undermined by the regulations. The harmonized regulations may ensure the safe development of therapies with cells manufactured with industrial production, whether with hESCs or with induced pluripotent stem cells (iPSCs) as starting material. But the breadth of possible cellular therapies is effectively narrowed down to options that necessitate intensive laboratory cultivation, while autologous procedures remain unproven. This means that the regulations do not work in the best interests of patients and clinicians, and the unavailability of evidence-based autologous ther-

apies is an indicator of this problem. Thus, the European harmonized regulations in effect counteract some of the ethical motives for these regulations, as well as the aims of political and economic integration for a coordinated approach to scientific and clinical excellence in biomedicine in Europe.

Regulation of Stem Cell Clinical Trials and Closure of Treatment Routes

All stem cell clinical trials in Europe have to comply with a set of rules including two major directives, namely the EU Clinical Trials Directive (EUCTD 2001/20) and its successor regulation, the EU Tissue and Cells Directive (EUTCD 2004/23/EC). The latter is made up of three directives: the parent directive, which provides the framework legislation, and two technical directives, which spell out technical requirements for the ways in which cells are to be handled. The EUTCD distinguishes two types of cell therapies. First are the so-called somatic cell therapies, with established uses of human stem cells in medicine—for example, bone marrow transplantation in oncology—for which there are defined standards already largely complied with by European blood donor, transfusion, and hematology laboratory networks. Second are cell therapies with so-called advanced therapy medicinal products (ATMP). Cell therapies are advanced medicinal products, when there is (1) substantial manipulation of any cell type (which in the case of selection for size by cell separation is not a somatic cell product; see EMA 2015), or (2) when the intended use of the cells is non-homologous—that is, when it is different to the cells' normal function in the body (Doherty 2015). This category includes laboratory-created products based on genes, cells, or tissue engineering—in other words, new forms of cells used in medicine that as such require far more stringent regulation and standards. ATMPs can only be produced and used under very closely defined and recorded conditions in the laboratory, in the clinic, and on the route between them (EMA 2017). ATMPs include novel applications and cell products for new forms of cell-based treatments. For example, established applications of allogeneic and autologous bone marrow transplants in cancer therapy are classified as somatic cells therapies, not ATMP, whereas the autologous application of bone marrow–derived stem cells into the coronary artery was classified as an ATMP in 2010 (CAT 2010).

In effect, this specific act of reclassifying autologous bone marrow stem cells applied in the heart as an ATMP has undermined the finances of the first phase III stem cell trial funded by the European Commission. Begun in 2011, the BAMI trial—an abbreviation for "The effect of intracoronary reinfusion of bone marrow-derived mononuclear cells (BM-MNC) on all-cause mortality in acute myocardial infarction"—is a multinational clinical trial in 11 EU countries. The purpose of the trial is to test the efficacy of this stem cell application in myocardial infarction (Lovell and Mathur 2010; Mathur et al. 2017). The medical procedure

involves aspirating bone marrow from the patient after standard acute myocardial infarction (AMI) treatment, sorting the bone marrow aspirate by size (filtering it) to have a concentration of the larger mesenchymal stem cells, and reinjecting those larger stem cells into the bloodstream of the patient.

BAMI provides an especially illuminating perspective on the financial impact of regulatory change, in that it was costed in one regulatory environment yet is being conducted in another. In the BAMI meetings and in interviews conducted with BAMI clinicians during my long-term research project within that large consortium, many questioned whether the separation of the bone marrow aspirate into smaller and larger cells and its reinjection into the donor's coronary artery could be classified as a substantially manipulated cell use in non-homologous application. Note that the reinjection of such bone marrow cells into the circulation has previously been shown to be safe. From 2004 onwards, phase I and II trials using the BAMI procedure were categorized differently: in some countries (such as Germany), the procedure was categorized as an ATMP; in other countries (such as the UK), these trials were conducted following the less demanding somatic cell therapy regulations (Weber, Wilson-Kovacs, and Hauskeller 2010; Wilson-Kovacs, Weber, and Hauskeller 2010). Regarding the two criteria for ATMP—namely that a cell therapy uses a product made from human cells, genes, or tissues, and that its application is novel non-homologous use, as opposed to the role the cells usually have in the body—the BAMI procedure (as the clinicians categorize it based on their collective professional and expert opinion) is ambiguous. Cell sorting by size is not seen as a substantial manipulation, and whether the reinjection of bone marrow stem cells into the blood stream is non-homologous use can be questioned, because it is so similar to the somatic cell therapies in oncology. On top of that, the novelty of the procedure in 2010 can be called into question, because the BAMI procedure was thoroughly tested in terms of safety and feasibility by the time the Committee for Advanced Therapies (CAT) decided to reclassify that procedure as ATMP.

The major effect of the reclassification was that the practice conditions and institutional infrastructures for the BAMI procedure changed. Before the implementation rules of the EUTCD were harmonized and the CAT established, somatic cell research could be conducted in many European countries under somatic cell therapy regulations. Clinicians conducting trials with autologous or somatic stem cells classified as somatic cell therapy often used the laboratories, banking, and international transport routes of the local hematology laboratory and blood donation and transfusion services.

BAMI started in 2011 with a grant in the Framework Programme 7 (FP7) of almost €6 million. It is a blinded randomized controlled clinical trial that aimed to recruit 3,000 patients, with 1,500 having the BMSC reinjection. When the principal investigators budgeted the EU FP7 funding application, the assumption was that—with the organizational costs for setting up national coordinating

centres, monitoring procedures, central infrastructure such as the randomization procedure, and so forth—there would be €947 available for the recruitment and treatment of each patient-participant. Then, in 2011, the rules changed for how the procedure had to be conducted. Specifically, the filtered bone marrow aspirate had been designated as an ATMP. It took time to discover quite how this would affect patient recruitment. Under the new regulations, fully qualified laboratories and staff were available only in three of the 11 partner countries. Hence, the hospitals recruiting patients to BAMI all across Europe had to send their cells to one of those three laboratories. It was difficult to establish the routines to be followed in order to transport the bone marrow aspirate for filtering between the hospital and the laboratories within a tight timeframe and across long distances (Hauskeller and Baur 2017).

The cell processing locations needed their regulator's approval for transporting cells to other countries, and travel routes compliant with the ATMP regulations had to be arranged. The cost of sending the bone marrow aspirate to one of the three approved laboratories ran to around €500 each. The procedure itself used in the cell processing laboratories in BAMI is currently estimated at a nonprofit price of €500 per unit. (Commercial laboratories might calculate and indeed face much higher costs.) Thus, together, the transportation and laboratory processing of the cells cost more than what is available per patient. Furthermore, other costs come from training standards and so forth that are part of the EUTCD and ATMP regulation. This means the amount per patient was exceeded without any budget remaining for staff costs on site, additional patient days in hospital, costs for translators, or other needs that might arise from what I have called cultural differences (Hauskeller, Baur, and Harrington 2017). As a publicly funded academic trial, costs in BAMI were calculated without profit margins, and a tight budget of €6 million seemed feasible, otherwise the European Commission would not have provided its funding. However, under ATMP conditions, the three laboratories BAMI had access to in 2011 had to be used throughout. Although many new ATMP certified laboratories opened near BAMI recruiting hospitals, the high fees and service charges requested by these new laboratories made their use unaffordable.

Ethical and Structural Implications of the Regulations for Autologous Stem Cells

The sociological findings from a study on the first phase III stem cell trial in Europe have been reported in detail elsewhere (Hauskeller and Baur 2017; Hauskeller, Baur, and Harrington 2017). Here I draw out the ethical and structural effects of the regulations in place for autologous and somatic stem cell research and its clinical translation, focusing on four aspects. First, patients might be pushed toward a growing direct-to-consumer market, where such unproven treatments

are on offer. Second, the higher costs for research and treatments if they come into the clinic can be an obstacle to clinical uptake and thus patient access. Third, the regulations effectively limit clinician-led academic research, so that clinical approaches that are not aligned with industry interests can hardly be pursued for practical and financial reasons. Fourth, this implies that the regulations appear biased in favor of industry interests over those of patients and consumers. These four points signal contradictions between ethical and moral statements about stem cell therapies in diverse applications for the wider good on the one hand, and the big market- and economic advantage–oriented policies on the other. The effects of the current regulation on clinical trials with autologous SCBI, and on the creation of diverse markets for the storage and use of stem cells, indicate that economic policy weighs more heavily in shaping European regulations of stem cell research than do ethical and moral considerations.

The Conundrum of Efficacy versus Cost

It is likely that autologous SCBI will only come into the clinic as evidence-based if the research is funded by public sources. This is because there is little intellectual property in cell-based procedures, such as BAMI, and because they cannot be scaled up well. Industrial funders in the pharmaceutical sector want to create cell products, not cell procedures without revenue potential. The funding award by the European Commission indicates that the evidence of therapeutic potential of the BAMI procedures had been recognized in the peer review process to justify the investment. Yet, while the funding application was under consideration, CAT altered the conditions under which the project had seemed financially feasible, namely when practiced largely under somatic cell therapy (SCT) regulations—especially because SCT regulations would have allowed the use of the local hematology laboratories instead of ATMP certified laboratories.

What does this mean for the clinic when there is a multifold increase in cost for the translational research required to prepare the evidence base necessary for bringing autologous stem cell procedures such as BAMI that are in development? And how does this situation affect the prospect of the procedures ever becoming part of standard clinical care?

The UK's National Institute for Health and Care Excellence (NICE) and similar professional institutes in other European countries decide whether the cost-relative benefits of new therapies justify their inclusion in treatment protocols in national health-care systems. They judge a new drug, diagnostic test, medical procedure or treatment protocol by taking into account the scientific evidence for the efficacy of the health benefits gained and the costs and risks associated with it. Whether the procedure tested in BAMI does effectively extend the life of patients with acute myocardial infarction (AMI) remains to be seen. The trial is on-going. But the cost that the procedure would add to standard AMI treatment may help determine whether it will become part of standard treatment

if proven to be efficacious. The classification as ATMP adds to the cost of the trial, and ultimately to the cost of the treatment. Further, the efficacy of the procedure will have been demonstrated under ATMP conditions, and hence, the standard treatment would likely have to follow those same protocol standards as well. The balance between investment in staff, time, and laboratory processing costs, which the ATMP conditions add, raises the threshold of efficacy in extending patient survival and well-being. In other words, the effect in patients has to be quantifiably larger to justify clinical introduction given the cost—and from what is known to date from phase I and II trials, in AMI specifically, the effect of an autologous stem cell procedure, if evidenced, may not be large enough to justify the rather high additional cost.

This also means that the research itself may become ethically concerning, because at least part of the justification for research with patients is the potential that it becomes clinical therapy for the benefit of many. If treatments become much more expensive, the possibility that they will actually become available to many or all citizens with the relevant illness is reduced. Regulations are justified as providing safeguards for patients during research and in the general clinic, but if such regulation adds great cost for a comparatively small benefit, the therapies will not become part of system-wide approved standard treatment protocols. From this perspective, the regulation can harm patients because therapeutic options are either not investigated at all or not ultimately introduced into standard care.

Foreclosing Academic Research and Nonprofit Stem Cell Therapy Pathways

There are at least two other important consequences of creating such detailed, technically harmonized regulations in an international landscape that is diverse in its moral and ethical codes, its laws and health-care regimes, and in the development of high-caliber scientific and technological institutions. One relates to the actual added cost, which threatens to undermine academic, clinician-led research. The other is that researchers with good industrial connections and access to first-rate facilities are advantaged.

From the perspective of the clinicians and nurses working in BAMI, the events that unfolded were largely unexpected, and they had to invent many novel solutions to go ahead. BAMI is an academic trial, just as many phase I and phase II trials are, but it is on a much bigger scale, involving 21 institutions in 11 countries. As of 2017, BAMI has been recruiting patients in Belgium, the Czech Republic, Denmark, Finland, Germany, Italy, the Netherlands, Spain, and the UK. The motivation is clinically driven, and the people who lead and manage this trial are academic clinician scientists, based in university hospitals, and without a major industry sponsor. The role of the two small companies involved was in supporting infrastructural needs. As a whole, BAMI is an independent academic project. The clinicians leading it have developed the research base for this procedure, conducted phase I and phase II trials of the procedure, and found it worth

testing in a large efficacy trial. They have worked together for years to prepare it, finding that regardless of its efficacy, there is no interest from big pharmaceutical companies in a procedure that does not confer intellectual property to the treatment trialed.

BAMI encountered implementation problems from the beginning, resulting in a three-year expansion of the trial running time from five to now eight years. This itself has caused additional problems, because timely conduct is an important scientific factor that can disrupt a trial protocol. All the relevant treatment conditions surrounding the tested procedure, such as the standard treatment protocol for AMI, ideally should remain the same.

In the industry-sponsored phase III trials in which the nurses and clinicians usually take part, the pharmaceutical sponsor and an external clinical research organization (CRO) manage the regulatory problems that arise on site. The medical team just recruit patients and report what they do; the industrial sponsor sorts out any problems encountered in trial implementation on site. National coordinating center staff in BAMI highlighted the huge difference between running an industry-sponsored trial and the BAMI trial, which was being conducted by clinician-scientists without the expertise and funding backdrop the pharmaceutical industry provides for its trials (Hauskeller, Baur, and Harrington 2017). Many of the challenges faced in the day-to-day running of the multinational trial compared to a typical phase I and II trial were also unexpected by the team. Yet, they argue that this type of academic cooperation in trials is the only way in which such autologous stem cell procedures have a chance of getting tested for efficacy and efficiency and eventually entering into standard clinic care.

Regulations and the requirements demanded by local ethics committees add to the complex demands of running a phase III trial. The higher the levels for such elements as technological refinement and training of staff are set, the more demanding compliance with a harmonized regulatory rule set becomes. The fact that clinical teams in hospitals have to master those many tasks themselves makes participation in this research in Europe very costly. From this it can be concluded that the financial and organizational infrastructure for running such major academic trials needs to be improved. Access to the respective laboratories, trained staff, and equipment, and managing the regulatory and cultural particularities at national or regional levels requires commitment from either private institutional funders or from the state. In order to succeed, academic teams pursuing research pathways that are promising and depend on support from nonprofit or public institutions need the financial backing which BAMI enjoyed, but also logistical and CRO support.

The other and more hidden ethical issue arising from high barriers to conducting research because of regulation concerns equal access of research teams across Europe (and more generally between different parts of the world). BAMI has been affected by the lack of accessible local laboratories with so-called good

manufacturing process certification. At present, the cost of running these laboratories, however, and the commercial approach to renting out their services, make their use unfeasible for non-industry researchers. Also, for researchers in poorer countries or not in the vicinity of the industries that supply laboratory equipment and infrastructure, participation in research following these standards becomes especially hard. Access to research facilities is not evenly distributed across Europe, despite the EU's efforts at integration and close cooperation. The tight technical standards thereby restrict research to those with access to appropriate facilities. This may align perfectly with the competitive advantage targeted in the Lisbon and Europe 2020 strategies, but it can be challenged from an ethical perspective, especially when the price for the therapeutics is also high and thus limited to select health-care systems. The EU policies might achieve international competitive advantage but at the same time fail to equalize conditions for research intensity and excellence among its members.

Patients and Their Options

A key dimension of ethical concern in the scientific field of regenerative medicine is how patients may lose out. If the conditions prevent the production of evidence as to whether autologous SCBIs are efficacious, patients lose the possibility that they may improve their health at a low cost.

The foreclosure of particular research and translational pathways means that autologous procedures, such as that being evaluated in BAMI, are less likely to reach patients in the public health-care settings that are generally available in European countries. If patients and consumers become aware that such treatments are on offer—and the hope that SCBIs can be very beneficial has been widely advertised, not least to obtain research funding (Kamenova and Caulfield 2015)—then it is not surprising that hopeful patients seek them out. The debate summarized earlier about the growing direct-to-consumer market for unproven SCBIs is very critical of patients buying these services and of the clinicians who offer them. Yet if the regulatory and institutional policies in Europe are designed to make it not just a question of time until their efficacy is evidenced or refuted, but instead make it structurally unlikely that these pathways to better health will be proved, then patients may seek to get them anyway via the heavily criticized stem cell tourism industry (Lysagth et al. 2017; Petersen, Seear, and Munsie 2013; Sipp et al. 2017). The argument that only proven therapies should be offered stands on weak legs if credible potential therapies will not come into the clinic even when they seem promising, low risk, and when hundreds of patients have undergone them in phase I and II trials.

Patient activists ask that their moral rights to gain access to potentially life-saving treatments be respected, and the current regulatory bias can be seen as contradicting and effacing this right.

The tight regional regulations in the EU that work alongside the compulsory harmonized regulations of technical details in how to conduct trials mean that patients' interests exert a strong influence on the emerging therapy landscape and on the market for cell services and treatments. Interventions with somatic or autologous human or nonhuman cells that clinicians judge potentially beneficial but which have not been evidenced scientifically allow for compassionate use exemptions.

Thus the hurdles encountered by researchers who want to provide evidence of whether or not autologous stem cell procedures are efficacious open the door for the direct-to-consumer market. Reports of patients supposedly protected from harm through cell-based therapies fosters the growth of private medical services, where patients are subject to the risks of unproven cell injections and transplants. The existence of this market corresponds with the interests of the multitude of European small, medium, and large companies that produce the laboratory equipment used in the official world of research and medicine, and in the private sector of unproven medical experimentation. The economy-building aims of the Lisbon Strategy, as well as the aim for an inclusive economy in Europe 2020 to foster international cooperation, are well served with this effect, too. But patients and clinicians who want to see the balanced investment into different pathways to stem cell medicine are currently less well served.

This effect of a growing inter-European patchwork of private hospital offers for stem cell treatments presents a self-contradiction between the overall strategies of advancing this field and policies in the European Group on Ethics (EGE). The EGE has strongly argued against private markets in stem cell storage and medicine (Hauskeller and Beltrame 2016). It seems rather that market interests, at the forefront of both 10-year strategies, dominate over ethical and moral considerations. While ethical considerations may be highly visible and shape national policies and bioeconomies when national regulators consider which forms of stem cell research and collection are allowed on their territory, those considerations are eclipsed by the interaction of specific regulations, open borders for tissues to travel, and consumers to shop around the diverse service and market offers available in different European countries.

Conclusion

Studying the implementation of BAMI has shown that EU regulations are not neutral or objective toward stem cells in clinical application. The regulations' criteria, how they are defined, and the practices of decision-making with those criteria for what is regulated in which ways are crucial for development in biomedical science. These factors have consequences for who can conduct the kind of research that qualifies a new treatment as "proven" in its efficacy. The regulations also shape what kinds of therapies will be developed and come to market.

Market is obviously a Janus-faced term here, because the regulations prescribe the criteria for treatments that can be marketed as scientifically validated, but they also leave open routes to a large market of "unproven" treatments with cells that do not qualify and are collateral to the cell-based therapies the regulators guard as the regenerative medicine of the future.

I have laid out the background for the specific policies and regulations of research and medicine with human tissues and cells in Europe and how they have affected the first phase III clinical trial with autologous stem cells. The findings give many reasons why under existing conditions academic researchers in EU countries are unlikely to trial autologous cell therapies successfully and see them introduced subsequently. Patients who suffer, and clinicians who are convinced that autologous cell procedures can be a help to these patients, have the option, however, of entering the shadowy world of unproven treatments on the private market. The inflexible, generalizing and very costly European regulations may unintentionally serve to keep autologous cell applications in the obscure direct-to-consumer sphere. The alternative would be to have regulation that enables creating a solid evidence base for autologous stem cell treatments, and this would require a reconsideration of some of the current regulatory details, including which cells and applications should be classified as AMTPs.

The European set of harmonized standards requires advanced technological process control and thereby favors the industrial business model that aims at developing therapies with lab-produced cell products, rather than stem cell procedures. Some of the provisions counteract the development of alternative approaches such as somatic stem cells in autologous application. In consequence, safe and possibly efficacious procedures remain unevaluated and this provides a justification for offering them on the private market or claiming compassionate use. Many of these direct-to-consumer marketed procedures and applications are not as well-tested in phase I and II trials as are autologous bone marrow stem cells for heart disease, which puts patients at risk.

Looking at the overall picture of European regulations, the current regulatory regimes do not support either the best interests of patients or of the broad community of clinician-scientists and researchers. That is why, for ethical and scientific reasons, the European regulatory authorities should reconfigure their regulations to advance a fairer and more effective governance regime that advances all promising routes to cell-based therapies and procedures, and effectively curtail the harmful segments of the private market for cellular treatments.

References

Adriance, S. 2014. "Fighting for the 'Right to Try' Unapproved Drugs: Law as Persuasion." *Yale Law J Forum* 124: 148. http://www.yalelawjournal.org/forum/right-to-try-unapproved-drugs.

Beltrame, L. 2014. "The Political Economy of Umbilical Cord Blood Biobanking." In *Yearbook of the Institute for Advanced Studies on Science, Technology and Society*, ed. G. Getzinger, 63–81. Stade: Profil Verlag

Beltrame, L. 2018. "The Bioeconomies of Stem Cell Research." In *The Matrix of Stem Cell Research Revisited*, ed. C. Hauskeller, A. Pichl, and A. Manzeschke. Abingdon: Routledge, in press.

Bender, W., C. Hauskeller, and A. Manzei. 2006. *Crossing Borders: Ethical, Legal, Economic and Religious Views on Stem Cell Research*. Global Perspectives. Münster: Agenda Verlag.

Committee for Advanced Therapies (CAT). 2010. EMA/CAT657770/2010. Monthly Report, Oct. 2010.

Daley, G. Q., et al. 2016. "Setting Global Standards for Stem Cell Research and Clinical Translation: The 2016 ISSCR Guidelines." *ISSCR Stem Cell Rep* 6 (6): 787–97.

Doherty, K. 2015. "Regulation of Unproven Stem Cell Therapies: Medicinal Product or Medical Procedure?" *Eurostemcell*. http://www.eurostemcell.org/regulation-unproven-stem-cell-therapies-medicinal-product-or-medical-procedure.

European Committee of the Regions (ECR). 2010. "The Lisbon Strategy in Short." *European Monitoring Platform*. https://portal.cor.europa.eu/europe2020/Profiles/Pages/TheLisbonStrategyinshort.aspx.

European Group on Ethics in Science and New Technologies (EGE). 2007. "Recommendations on the Ethical Review of hESC FP7 Research Projects." *Opinion 22*. http://ec.europa.eu/archives/bepa/european-group-ethics/publications/opinions/index_en.htm.

European Medicines Agency (EMA). Committee for Advanced Therapies (CAT). 2015. *Reflection Paper on Classification of Advanced Therapy Medicinal Products*. 21 May 2015. E.MA/CAT/600280/2010 rev.1. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/06/WC500187744.pdf.

European Medicines Agency (EMA). 2017. Advanced Therapy Classification. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000296.jsp.

European Union Clinical Trials Directive (EUCTD). 2001. "Clinical Trial Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001." *Official J European Union* 1-5-2001, L 121/3M4. https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf.

European Union Clinical Trials Directive (EUCTD). 2004. "Tissue and Cells Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on Setting Standards of Quality and Safety for the Donation, Procurement, Testing, Processing, Preservation, Storage and Distribution of Human Tissues and Cells." *Official J European Union*. https://repository.library.georgetown.edu/handle/10822/991209.

EuroStemCell. 2017. "Regulations of Stem Cell Research in Europe." http://www.eurostemcell.org/regulation-stem-cell-research-europe.

Frischzellenkur. 2017. Online advert. http://www.frischzellen.de/index.php?id=35&L=2.

Hauskeller, C. 2004. "How Traditions of Ethical Reasoning and Institutional Processes Shape Stem Cell Research in the UK." *J Med Philos* 29 (5): 509–32.

Hauskeller, C., and L. Beltrame. 2016. "The Hybrid Bioeconomy of Umbilical Cord Blood Banking: Re-Examining the Narrative of Opposition Between Public and Private Services." *BioSocieties* 11: 415–34. DOI: 10.1057/biosoc.2015.45.

Hauskeller, C., and N. Baur. 2017. "Travelling Cells: Harmonized European Regulation and the BAMI Stem Cell Trial." In *Stem Cells in Clinical Application: Safety, Ethics and Regulation*, ed. P. Pham and A. Rosemann, 201–16. Cham: Springer.

Hauskeller, C., N. Baur, and J. Harrington. 2017. "Standards, Harmonization and Cultural Differences: Implementation of a European Stem Cell Clinical Trial." *Sci Cult*. DOI: 10.1080/09505431.2017.1347613.

International Society for Stem Cell Research (ISSCR). 2016. "Guidelines for Stem Cell Research and Clinical Translation." http://www.isscr.org/guidelines2016.

Joliff-Botrel, G., and P. Perrin. 2008. *Stem Cells: European Research Projects Involving Stem Cells in the 6th Framework Programme*. http://ec.europa.eu/research/fp6/p1/stemcells/pdf/stemcell_eu_research_fp6_en.pdf.

Kamenova, K., and T. Caulfield. 2015. "Stem Cell Hype: Media Portrayal of Therapy Translation." *Sci Transl Med* 7 (278): 278–84.

Kimmelman, J., et al. 2016. "New ISSCR Guidelines on the Ethics of Stem Cell Research." *Lancet*. 387: 1979–81. DOI: 10. 1016/S0140-6736(16)30390-7.

Liverani, M. 2011. "European Futures: The Politics and Practice of Research Policies in the European Union." PhD diss., University of Exeter.

Lovell, M. J., and A. Mathur. 2010. "Cardiac Stem Cell Therapy: Progress from the Bench to Bedside." *Heart* 96: 1531–37

Lysaght, T., et al. 2017. "The Deadly Business of an Unregulated Global Stem Cell Industry." *J Med Ethics*. https://www.medscape.com/medline/abstract/28356490.

Mathur, A., et al. 2017. "Consensus of the Task Force of the European Society of Cardiology Concerning the Clinical Investigation of the Use of Autologous Adult Stem Cells for Repair of the Heart: Update 2016." *Eur Heart J 38 (39): 2930–35.* DOI: 10.1093/eurheartj/ehw640.

Mendick, R., and A. Palmer. 2010. "Baby Death Scandal at a Stem Cell Clinic Which Treats Hundreds of British Patients a Year." *Telegraph,* 23 Oct. http://www.telegraph.co.uk/news/worldnews/europe/germany/8082935/Baby-death-scandal-at-stem-cell-clinic-which-treats-hundreds-of-British-patients-a-year.html.

Petersen, A., and K. Seear. 2011. "Technologies of Hope: Techniques of the Online Advertising of Stem Cell Treatments." *New Genet Soc* 30 (4): 329–46.

Petersen, A., K. Seear, and M. Munsie. 2013. "Therapeutic Journeys: The Hopeful Travails of Stem Cell Tourists." *Sociol Health Illn* 36 (5): 670–85.

Petersen, A., et al. 2017. *Stem Cell Tourism and the Political Economy of Hope*. London: Palgrave Macmillan.

Punzel, M. 2002. "Blutstammzellen: Hoffnungen für eine neue Medizin." In *Humane Stammzellen: Therapeutische Optionen, ökonomische Perspektiven, mediale Vermittlung*, ed. C. Hauskeller, 73–77. Lengerich: Pabst Science.

Raffaelli, R. 2018. "The Principle of Subsidiarity, European Parliament 2017." *Fact Sheets on the European Union*. http://www.europarl.europa.eu/ftu/pdf/en/FTU_1.2.2.pdf.

Ryan, K. A., et al. 2010. "Tracking the Rise of Stem Cell Tourism." *Regen Med* 5 (1): 27–33.

Salter, B. 2007. "Bioethics, Politics and the Moral Economy of human Embryonic Stem Cell Science: The Case of the European Union's Sixth Framework Programme." *New Genet Soc* 26 (3): 269–88.

Sipp, D., et al. 2017. "Marketing of Unproven Stem Cell-Based Interventions: A Call to Action." *Sci Transl Med* 9 (397). DOI: 10.1126/scitranslmed.aag0426.

Tanner, C., et al. 2018. "Big Promise, Big Business: The Sociocultural and Regulatory Dynamics of Stem Cell Tourism." In *The Matrix of Stem Cell Research Revisited*, ed. C. Hauskeller, A. Pichl, and A. Manzeschke. Abingdon: Routledge, in press.

Tuffs, A. 2010. "Stem Cell Treatment in Germany Is Under Scrutiny After Child's Death." *BMJ* 341:c6203. DOI: 10.1136/bmj.c6203.

Turner, L., and P. Knoepfler. 2016. "Selling Stem Cells in the USA: Assessing the Direct-to-Consumer Industry." *Cell Stem Cell* 19 (2): 154–57.

Weber, S., D. Wilson-Kovacs, and C. Hauskeller. 2010. "The Regulation of Stem Cell Therapies: Comparing the UK and Germany." In *Human Tissue Research,* ed. C. Lenk, et al., 159–67. Oxford: Oxford University Press.

Wilson-Kovacs, D., S. Weber, and C. Hauskeller. 2010. "Stem Cell Clinical Trials for Cardiac Repair: Regulation as Practical Accomplishment." *Sociol Health Illn* 32 (1): 89–105.