

ESF Exploratory Workshop EW 13-017:

Regulating Stem Cell-Based Regenerative Medicine: New Ethical Challenges for Europe

Toulouse (France), October 1 3, 2014

Convener:

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Scientific Report

Executive summary

Thanks to the financial support of the European Science Foundation, we have convened an Exploratory Workshop in the historical building of the Faculty of Medicine of the Paul Sabatier University in Toulouse (France). The aim of the workshop was to discuss the ethical, legal and social implications connected to the provision of yet unproven and unapproved stem cell-based therapies.

The science policy agenda of the last decade has had stem cells at its core in all countries that participate in the global knowledge economy: controversies spanned from the use, and consequent destruction of human embryos for research purposes, to the potential use of human cloning to create disease-specific stem cell lines, to the procurement of human eggs and the creation of human-animal chimera. Today however, new ethical and regulatory challenges emerge as scientist struggle to turn biological knowledge into stem cell-based regenerative medicine. In Europe, legislators, regulatory agencies and professionals are establishing specific policies and guidelines to allow the development of stem cell-based regenerative medicine while protecting research subjects and patients from the risks connected to it. Recent judicial and executive decisions allowed the use of unproven stem cell treatments to seriously diseased children in Italy (Sentence 30.8.2012, Tribunal of Venice, proc. ex art. 700 CPC *ante causam* Carrer Celeste; Ministerial Decree March 25, 2013, n. 24 by the Minister of Health). Albeit the scientific community vigorously opposed these decisions, the general public seems to support them in the name of getting access to new technologies. As some commentators also suggested, should they be denied access to those unproven therapies, patients might try to go abroad, to obtain the same service in more permissive countries. Stem cell therapy tourism might be fostered due to legal and regulatory decisions. This case illustrates that stem cell medicine poses significant ethical challenges and that sound ethical reflection is needed to advance scientific progress in a responsible way.

With few exceptions, the debate on the ethics of unproven therapies and stem cell tourism has been limited to North America so far. Therefore, this ESF exploratory workshop was meant to

discuss the existing regulatory framework of stem cell-based medicine in Europe in order to highlight its ethical implications, including its intended and unintended consequences from a new perspective.

We convened an interdisciplinary panel of 16 experts coming from different backgrounds. Unfortunately, one of the invited participants could not join us due to health related problems and therefore the group was finally made of 15 participants in total.

The majority of the participants were academics (13 out of 15), but they came from a variety of disciplines as we had 3 lawyers, 1 philosopher, 5 scientists working in the field of biomedicine, 2 social scientists, 2 political scientists. Moreover, we had 1 member of a patients' advocacy group, 1 regulator and 1 officer of Europe's major funder of scientific research (the European Commission).

The workshop was therefore an excellent occasion to share information concerning the current state of the regulatory framework that governs the translation of stem cells into clinical products in Europe and to discuss the future directions of the field in the light of recent controversies.

In particular, four major points were highlighted during the discussions.

- First, that investment of the translation of stem cells into regenerative medicine products will continue to be sustained thanks to both private and public funding, as this field is emphasized also within the Horizon2020 program.
- Secondly, there is a potential tension between the legitimate push to deliver new health products to the market and the necessity to assure that those products respond to rigorous criteria of safety and efficacy. In this respect, the panel stressed that current emphasis on the therapeutic potential of stem cell-based regenerative medicine is largely speculative – a fact that calls for more responsible communication concerning the advancement of science in this field. Furthermore, the hype that surrounds this field brings about an unconscious minimization of the risks connected to clinical experimentation with stem cells.
- Third, looking deeply at the debates over the regulation and the governance of regenerative medicine products there are signs of a changing cultural attitude in the domain of health care: different actors, including providers, regulators and patients, are increasingly adopting a consumerist stance with respect to the provision of health

care services and products. Such a cultural shift – which represents a departure from the conventional ethical model of public health that inspires most European health care systems - runs the risk of being reinforced by the current model of innovation in regenerative medicine. Phenomena such as stem cell travels (or tourism) as well as the growing offer of unproven stem cell therapies represent only the most visible effect of such cultural change.

- Fourth, the definition and the categorization of stem cells “products” remain unclear and are subject to various interpretations depending on the various stakeholders. This legal “uncertainty” challenges the scientific strategies to adopt in order to speed up the access of the “products” to the market.

From a pragmatic point of view, the workshop highlighted that certain ambiguities in the European Regulation 1394/2007 on the centralized marketing approval for advanced therapy medicinal products, should be resolved. In particular, the hospital exemption clause (art. 28) creates a shortcut to the clinical trial pipeline that is not necessarily justified, neither at the scientific, nor at the ethical level.

Scientific content of the event

The workshop has been an opportunity to discuss the new ethical challenges raised by stem cell based regenerative medicine from an interdisciplinary perspective. As a consequence, much of the presentations and much of the discussions that they generated, revolved around of the regulatory issues that surround the development of stem cell-based regenerative medicine.

Among the aims of the workshop we also wanted to stimulate the formation of a new research agenda to foster a European debate about the regulatory challenges that lay ahead the realization of the much-awaited promise of stem cell science. In this last respect, the workshop represented an occasion in two senses.

First of all, it allowed participants to brainstorm their ideas and views on the topic. We decided that, for such an activity to be fully productive, discussion had to take place without too rigidly specified disciplinary boundaries. Although each of the participants was coming from a well-defined academic background, the diversity in the composition of the group, almost automatically, fostered a climate of openness and contamination that, we think, was beneficial precisely to the *exploratory* character of the event.

Second, the workshop allowed us to test whether a diverse panel of experts could identify a number of core themes of common interest that are worth being further explored. On this second point, we noticed that discussions kept on insisting on a defined number of topics. Indeed participants have recognized at least the following four themes as meriting greater scholarly attention:

- the scientific controversies concerning the presumed and actual biological and therapeutic properties of different types of stem cells.
- the tensions between evidence-based medicine and more empirical approaches to innovation;
- the emphasis on accelerated innovation and early access to biomedical novelties as a marker of a specific culture of risk;

- the evolution of funding and regulatory policies aimed at accelerating innovation and its effects on the practice of science and medicine.

Each of the above themes lends itself to be regarded under the angle of a specific discipline, from molecular biology to bioethics, from science and technology studies to law and political sciences. As we said, however, during the workshop we did not attempt to articulate our regulatory discourse around a specific disciplinary thread. Rather, as anticipated in our application, we left participants free to bring on the table their own disciplinary contribution. This was indeed a fruitful exercise, as participants from different backgrounds tried to recast problems in their specific scholarly terms. We can thus conclude that the exploratory nature of this event was fully realized thanks to the interdisciplinary character of the workshop. There was indeed contamination, but also the realization that each discipline – at least among those represented at the workshop – can provide a methodologically solid contribution to the themes specified above. The objective of visualizing a potentially new research agenda, was therefore successfully attained. Also, and not less important, we raised awareness among participants concerning the importance of the ethical and regulatory stakes in regenerative medicine and in biomedicine more in general.

On the first day, the opening keynote speech by Prof. Paolo Bianco addressed key elements of the phenomenon of stem cell tourism and of the ever-expanding offer of unproven treatments based on stem cells. By illustrating a number of case studies, Prof. Bianco eventually explained that the provision of stem cell treatments ahead of clinical validation pertains to a specific kind of cells: mesenchymal stem cells (MSCs). The latter are currently the object of the vast majority of clinical trials in the field of regenerative medicine and therefore represent the main asset on this emerging market. As a consequence, exploiting the hype that surrounds this field, it is mesenchymal stem cells that unscrupulous providers offer to their patients, even if their therapeutic potential is far from being proven. According to Prof. Bianco, scientists, and especially those who have a direct interest in the development of MSC-based products, deliberately exaggerate the biological and therapeutic potential of these cells. Scientific and economic issues are therefore deeply interconnected and should be analyzed jointly. The keynote successfully set the tone for the subsequent discussions.

The three other talks of the morning analyzed, respectively, the legal, ethical and translational implications of EU Regulation 1394/2007 and provided further elements for that occupied the rest of the workshop.

After the three explanatory talks, the main group was divided in two sub-groups – and not in three as originally foreseen. This decision was taken due to the total number of participants, to avoid that, in smaller groups, the views of one or two participants could have overridden those of the others. One group was led by Alessandro Blasimme and discussed the ethical issues of stem cell tourism and the culture of risk in innovative clinical research. The other group, led by Emmanuelle Rial-Sebbag, focused on the political and regulatory challenges of innovation.

As the group of participants reunited, the two leaders gave a summary of the work of the sub-group and a fruitful discussion followed suite.

Reasoning on the rationale for expanded access programs, the group highlighted the dominance of a free choice ethical paradigm in the domain of not fully proven cures. This cultural paradigm is based on an ideology of rational choice whereby patients are individually in charge of assessing the risk and benefits of therapies that are, in one way or another, available on the market of health goods. This logic embodies an individualistic conception of risk – typical of late-capitalist societies, according to some. Such a cultural orientation can enter in tension with the collectivist assumptions of a public health model of risk.

The group noticed, moreover, that in the debate on the hype and excessive expectations that surround stem cell medicine, commentators recurrently highlight the necessity to provide patients with more, and more accurate, information. The group obviously shared this view, but noticed that it buys into the same consumer logic that it seeks to debunk.

An interesting element of the narrative that sustains this logic is represented by what the group has termed the dilemmas of giving up. Most of the regulatory instruments that allow access to not fully validated therapies, as well as a large part of the offer of unproven stem cells is directed towards patients who have exhausted all other therapeutic options. For these patients, passively accepting their clinical condition is very hard. For this reason, some of them (or their families) are willing to try anything they can to combat their disease. This attitude is understandable and could potentially be explained by reference to its cultural constituents. However, such a radical form of engagement with the biographic condition of

being diseased may have negative effects – both physical, psychological and financial – that deserve closer ethical scrutiny. The idea that patients who have exhausted their therapeutic options just simply have nothing to lose and therefore should be granted access to whatever therapy or pseudo-therapy they are willing to accept is an over-simplification. The “nothing to lose” argument does not do justice to the complexity of human experience in such hard circumstances and runs the risk of underestimating specific forms of vulnerability to exploitation in favor of a way too speculative respect for individual autonomy and therapeutic hope, to the extent that such autonomy could lead to social isolation, trauma and harm, and could foreclose other options and other ways of coping with the disease. In particular, the group noticed that it is necessary to imagine new pathways or platforms of care for those patients, possibly offering them alternative ways of making sense of their condition with the aid and dedicated support of specialized personnel and of other patients.

One participant (Prof. Klaus Hoyer) noticed that, in general, the Kantian vision of morality as self-restraint is no longer regarded as valid. Such an orientation plays out specifically in the domain of health care. In this area of human practice, a growing emphasis on personal responsibility with respect to health creates the conditions for individual agency to be understood as a cultural and social norm. In such cultural circumstances, giving up one’s efforts to combat a condition just does not look like a viable option, even in the case of diseases that medicine cannot currently cure or treat.

A further theme of discussion was represented by the politics of science funding. The group recognized that current funding mechanisms for academic science project on scientific research the economic imperatives of innovation strategies that do not necessarily fit well with the epistemic rules of the scientific community. As it is well-known, the scarcity of fixed, long-term funds for university research and the spread on the grant mechanism instilled a competitive logic within science. If on the one hand this may have stimulated competition and productivity, on the other it has systematically forced scientists to oversell their research to both grant agencies and to the public at large. The group recognized therefore that, on top of the greed of commercially oriented actors and of the misrepresentation of science by the press, scientists themselves have a responsibility in the way science is presented, and consequently interpreted and re-imagined, within society. Uncertainties are always minimized, if not hidden, and those preliminary results that may possess even a remote therapeutic potential are sold as being directly conducive to much-awaited applications. However, as any scientist knows, the process that brings scientific knowledge from the bench

of the lab to the bed of the patient is much more complex and uncertain than that. Most importantly in this respect, the translation of scientific knowledge into cures is generally destined to pass through multiple rounds of failures before a molecule or a new therapeutic product can be proven to work. And yet, science policy is deliberately oriented towards the promotion of a distorted image of the scientific enterprise. It should not thus strike one as a surprise if the public is ready to accept totally invalid treatments as legitimate cures.

On day two, discussions focused on the regulatory themes that could be of relevance for a possible practical intervention aimed at reducing the risk of excessive hype regarding new therapies. Prof. Luca Pani highlighted how insistence on individual choice as a justification for allowing patients to access unproven therapies is a strongly rhetorical argument. In reality, these patients can hardly be said to be empowered, in the sense of exercising their power of choice. In the absence of adequate informed consent procedures, or in the case of infants and minors, or when there are contrasts between the parents as to the opportunity to resort to unproven therapies, the treatment that these patients finally access cannot be reasonably considered as the object of deliberate choice. The group further stressed that, in principle, interference with individual therapeutic choice may be justified by the fact that illicit exploitation can take place even (and probably especially) in the case of patients that no longer have any approved therapy to try. In this respect, ethics committees should be careful, and probably receive guidance from regulatory agencies and professional associations, as to how to assess risks and benefits in the case of expanded access to experimental therapies or in the case of off-label use of innovative ones. In the absence of clear and protective provisions of this kind, a regulatory possibility like the hospital exemption (art. 28 of the EU Regulation 1394/2007) runs the risk of representing an open door to ethically unacceptable and scientifically dubious practices. As a consequence, this part of the Regulation, some participants strongly argued, should be reformed if not suppressed.

Assessment of the results, contribution to the future direction of the field, outcome

When we thought of reassembling together such an heterogeneous group of scholars and professionals to discuss a theme of such great significance, we hoped that disciplinary barriers would have not hampered the discussion and that contamination could have been productive. We were happy to notice that – contrary to what is too often the case – the discussion was always characterized by a climate of cultural openness and curiosity rather than by biased hostility. Such an outcome was far from obvious, but it was attained rather naturally nonetheless.

Indeed, we are satisfied by the degree of interaction testified both by the discussions and by the informal conversations that went on incessantly over coffee breaks and meals. The themes that the group highlighted as the most relevant, in our view, form the core of a potentially very interesting and coherent research agenda. From this point of view, we were delighted to see that our initial idea has yielded the expected fruits. During the last session of the workshop, the group discussed possible follow up activities. In particular, following the indication of the participants, we have decided to propose three editorial activities:

1. A commentary piece could be submitted by the conveners to a high-impact journal, to maximize the visibility of the event and the importance of the themes that we discussed during the workshop.
2. Some participants (Paolo Bianco, Luca Pani and Alessandro Blasimme) proposed to write a specific paper on the Hospital Exemption rule included in Regulation EC 1394/2007.
3. The organizers and the participants agreed on the possibility of contacting a journal to propose a special issue to be coordinated by the conveners.

The introductory piece will highlight the trade-offs that currently emerge in the clinical translation of regenerative medicine, in particular: the scientific controversies; the

tensions between evidence-based innovation and more empirical approaches; the emphasis on accelerated innovation and early access to biomedical novelties; the evolution of funding and regulatory tools to accommodate innovation.

Statistics

Age brackets

Under 35 = 2

35-50 = 6

Over 50 = 8

Country of origin

France = 5

Italy = 3

Germany = 3

The Netherland = 1

UK = 1

Spain = 1

Denmark = 1

Austria = 1

Gender:

Men = 9

Women = 7

Disciplines:

3 lawyers, 1 philosopher, 5 scientists working in the field of biomedicine, 2 social scientists, 2 political scientists, 1 member of a patients' advocacy group, 1 regulator and 1 officer the European Commission.

Final programme

Wednesday, October 1, 2014

Afternoon/Evening *Arrival and Registration (at the Crowne Plaza Hotel)*

20.00 *Dinner (restaurant Crowne Plaza Hotel)*

Thursday, October 2, 2014

08.30-08.40 **Welcome by Convener**

Emmanuelle Rial-Sebbag (UMR U 1027, Inserm, Univ. Toulouse III – Paul Sabatier, FR)

08.40-08.55 **Presentation of the European Science Foundation (ESF)**

Isabel Varela-Nieto (Scientific Review Group for the Bio-Medical Sciences)

08.55-09.00 Introductions of the participants

09.00-09.45 **Keynote “Stem Cells and Innovation: Economics, Policies, Ideology”**

Paolo Bianco (“Sapienza” University of Rome - Italy)

Session 1: Making Sense of the Regulatory Environment (Chair: Bianca Buechner)

09.50-10.05 **European Regulation No. 1394/2007: Legal principles and regulatory challenges**

Judit Sandor (Central European University (CEU) - Budapest)

10.10-10.25 **European Regulation No. 1394/2007: The Ethics Behind it.**

Alessandro Blasimme (UMR 1027 Inserm, Université Paul Sabatier, Toulouse – France)

- 10.30-10.45 Coffe/Tea Break
- 10.50-11.05 **European Regulation No. 1394/2007: Effects on Translational Science”**
Luc Sensebe (UMR5273, CNRS, ESF, INSERM, Université Paul Sabatier, Toulouse – France)
- 11.10-11.40 **Panel: Questions and Answers; Discussion about Strengths, Weaknesses, and Problems.**
- Session 2: Braking Boundaries (Chair: Bianca Buechner)**
- 11.45-12.50 **Interdisciplinary Working Groups:**
- **Group 1: Practical and ethical trade-offs in regulating stem cell tourism.**
Chair: Bianca Buechner (CELLS, University of Hannover, Germany)
 - **Group 2: New frontiers in the ethics of clinical research risks.**
Chair: Alessandro Blasimme (UMR U 1027, Inserm, Univ. Toulouse III – Paul Sabatier, France)
 - **Group 3: The politics of innovation between promise and uncertainty.**
Chair: Emmanuelle Rial-Sebbag (UMR U 1027, Inserm, Univ. Toulouse III – Paul Sabatier, France)
- 13.00 -14.00 *Lunch*
- 14.10 -15.30 **Interdisciplinary Working Groups. Reprise**
- 15.30 -15.50 *Coffee / tea break*

Session 3 **Constructing Convergence.** (Chair: Emmanuelle Rial-Sebbag)

15.50 -16.35 **Presentation of the Working Group Results (each 15 min.)**

16.35 -17.30 **General Discussion/Round Table: Perspectives and solutions based on the outcome of the working groups.**

19.45 *Networking Dinner*

Friday, October 3, 2014

Session 4: **Advancing the Regulatory Frontier.** (Chair: Alessandro Blasimme)

09.40 -10.00 **Resumé of WGs outcomes and of general discussion**

Bianca Buechner (University of Hannover, Germany)

10.00 -11.00 **Collective drafting of recommendations for regulatory changes.**

11.00 -11.15 *Coffee / Tea Break*

11.15 -12.15 **Collective drafting of recommendations for regulatory changes.**

Reprise

12.15 -12.50 **Discussion: Follow-up activities, collaborations, future meetings.**

12.50-13.00 **Closing Remarks.**

Emmanuelle Rial-Sebbag (UMR U 1027, Inserm, Univ. Toulouse III – Paul Sabatier, FR)

13.00-15.00 *Lunch, Networking.*

15.00 *End of the Workshop and departure*

Final list of participants

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